FORMULATION EVALUATION AND *IN VITRO* PERMEATION STUDIES OF TRANSDERMAL GLYBURIDE FROM MATRIX TYPE PATCHES AND PLO GELS

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Certificate

This is to certify that the dissertation entitled **"FORMULATION EVALUATION AND *IN VITRO* PERMEATION STUDIES OF TRANSDERMAL GLYBURIDE FROM MATRIX TYPE PATCHES AND PLO GELS"** was carried out by **S. DAPHNE SHERINE**, in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and complete satisfaction.

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CONTENTS

ABBREVIATIONS

TDDS system.	:	Transdermal drug delivery
PVA	:	Poly vinyl alcohol
PVP	:	Poly vinyl pyrrolidone
EC	:	Ethyl cellulose
HPMC cellulose	:	Hydroxypropyl methyl
PLO	:	Pluronic lecithin organogel
IPP	:	Isopropyl palmitate
DMSO	:	Dimethyl sulfoxide
SLS	:	Sodium lauryl sulfate
FT- IR	:	Fourier transform- infrared
CMC cellulose	:	Carboxymethyl
UV	:	Ultra Violet
IV	:	intra venous
USP Pharmacopeia	:	United States
NF	:	National formulary
IPM	:	Isopropyl myristate
PSA	:	Pressure-sensitive adhesives
PEG	:	Polyethylene glycol
DM	:	Diabetes mellitus

NIDDM	:	Non insulin dependent diabetes mellitus
IDDM	:	Insulin dependent diabetes mellitus.
RP-HPLC	:	Reverse phase high performance liquid chromatography

INTRODUCTION

In the past, the delivery of medications transdermally to a patient has been limited to administration by transcutaneous injection or by transdermal migration from a patch placed on the outer surface of the patient's skin. It has recently become evident that the benefits of i.v can be duplicated using skin as a drug delivery route[1]. It has been necessary for the TDDS to meet two requirements. First, the method must provide for extended containment of the drug and any carrier while placed on the patient's skin, in a form that does not lend itself either to contamination of the medication and carrier or to loss of the medication and carrier. Second, the systems employed must provide for a regulated and predictable rate of transfer of the medication (with or without the carrier) from the containment device into and through at least some layers of skin to where the medication will be dispersed throughout the affected area of the body[2].

Over the last two decades more than 35 transdermal patch products have been approved in US. In 2004 patch sales in the US were approximately $3.4 billion. Prescriptions for transdermal products have been used by ~12 million people worldwide.

Historical Perspecitve

Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. The mustard plaster, applied as a home remedy for severe chest congestion, may be considered as an example. Powdered mustard seed *(Brassica nigr*a) was mixed with warm water, and the resulting paste was spread on a strip of flannel, which was applied to the patient's chest with a cloth binding wrapped around the body to hold the plaster in place. The moisture and body warmth activated an enzyme (myrosin) in the mustard that hydrolyzed a glycoside (sinigrin), causing the release of the pungent active ingredient allyl isothio-cyanate[3]. The flannel served as an impermeable backing and the mustard paste was the reservoir. In addition to mustard plasters, several other plasters were recognized in early 20th century editions of the United States Pharmacopeia (USP) and National Formulary (NF). At one time, Belladonna Plaster, containing 0.25–0.30% of belladonna root alkaloids, was believed to act transdermally as an analgesic[4].

The first transdermal system for systemic delivery—a three-day patch that delivers scopolamine to treat motion sickness—was approved for use in the United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the public in general. Between 1979 and 2002,

a new patch was approved on average every 2.2 years. In 2003–2007, that rate has more than tripled to a new transdermal delivery system every 7.5 months. It is estimated that more than one billion transdermal patches are currently manufactured each year.

First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, non-cavitational ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound[5.]

TECHNOLOGIES UNDER DEVELOPMENT

The technologies currently under development can be divided into two broad categories.

Iontophoresis, The ability of an electric current to cause charged particles to move. A pair of adjacent electrodes placed on the skin set up an electrical potential between the skin and the capillaries below. At the positive electrode, positively charged drug molecules are driven away from the skin's surface toward the capillaries. Conversely, negatively charged drug molecules would be forced through the skin at the negative

electrode. It has the potential to expand the range of compounds available for transdermal delivery because the current can be literally switched on and off and modified, iontophoretic delivery enables rapid onset and offset, and drug delivery is highly controllable and programmable.

Poration technologies, uses high-frequency pulses of energy, in a variety of forms, temporarily to disrupt the stratum corneum, the layer of skin that stops many drug molecules crossing into the bloodstream. It is important to note that unlike iontophoresis, the energy used in poration technologies is not used to transport the drug across the skin, but facilitates its movement. Poration provides a "window" through which drug substances can pass much more readily and rapidly than they would normally[6].

Passive [7]

Matrix (Oxytrol, Vivelle Dot)

Reservoir (Androderm, Duragesic)

Active

Iontophoresis

Electroporation

Sonophoresis

Heat or thermal energy

Microneedle

Figure.1: ADVANCE DEVELOPMENT IN TDDS

PLO:

Pluronic lecithin organogel is a micro emulsion-based gel that has been effectively used by physicians and pharmacists to deliver hydrophilic and lipophilic drugs topically and transdermally across the stratum corneum. It is thermodynamically stable, viscoelastic, and biocompatible gel composed of phospholipids (lecithin), organic solvent, and polar solvent. Various types of therapeutic agents have been easily incorporated in PLO to improve their topical drug delivery. PLO improves the topical administration of drug mainly because of desired drug partitioning, biphasic drug solubility, and the modification of skin barrier system by organogel components. Beside this, it shows low skin irritation, increases patient compliance, reduces side effects, avoids first pass metabolism, and increases efficiency of drug. In addition, PLO has been shown *in vivo* and *in vitro* to modulate the release and permeation of drugs applied transdermally. Thus, in future, it has wide range of applications and opportunities to experiment with various drugs in this type of drug delivery system[8].One thing that seems clear is that the lecithin component of the PLO has the ability to act as an amphoteric surfactant and enables many drugs to penetrate the dermal layer[9].

History:

PLO is currently generating great interest in US as a topical and transdermal drug delivery vehicle. PLO- based drug containing formulations have not yet been marketed commercially. This may be because the evidence, to date, for its efficiency as, a transdermal vehicle is mainly anecdotal. Systemic scientific evidence is limited and little is known about its physicochemical properties as a result of the vehicle not has been studied in detail in research laboratories.

In the early 1990's, PLO was developed as a topical and transdermal drug delivery vehicle from the original LO's by Marty Jones, an American compounding pharmacist, and his colleague. They prepared the original LO's by adding small amounts of water to an organic solution of lecithin. PLO was then produced when they added an aqueous solution of Pluronic F127 (a tri-block copolymer, composed of polypropylene oxide, sandwiched between two polyethylene oxide units) to the original gel in an attempt to stabilize it. Collaborations between local physicians, their patients and the two pharmacists led to the incorporation of a number of drugs into PLO and anecdotal evidence of its efficacy as a transdermal delivery vehicle. Since then, interest in PLO for use in man and animals, especially cats, has increased dramatically and a range of drugs have been incorporated within PLO. As well as its used as a TDDS, PLO

has been investigated and suggested as a vehicle for application to the oral cavity [9,10]

Areas of application

The site of application can drastically affect the distribution and absorption of a drug.

If a systemic effect is desired, the gel should be applied to neck, inner thigh, or inner wrist area.

For a local effect**,** the gel should be applied directly to the joint or painful region.

Components of PLO Gel

Pluronic F-127:

Pluronic F-27 is mainly used as an emulsifying agent, solubilizing agent, and wetting agent between 15% and 50% concentration. It has the unique property of being solid at room temperature and liquid at low temperature. Thus, on contacting to skin, it forms gel and facilitate proper inunction and adhesion.

Soya lecithin:

Lecithin is a naturally occurring mixture of diglycerides of stearic, palmitic, and oleic acids linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine. Lecithin is thought to be a permeation enhancer as it increases the fluidity

of the epidermis, *stratum corneum*. It is used as dispersing, emulsifying, and stabilizing agent.

Water (H_2O):

Water acts as a stabilizing and structure-forming agent in the process of PLO formation. It is also used for solubilizing the Pluronic F-127 and polar drugs.

Isopropyl palmitate (IPP) or isopropyl myristate (IPM):

Acts as a non-oleaginous emollient with very good spreading ability and used for solubilizing the lecithin. It is a clear, colorless, practically odorless viscous liquid which solidifies at low temperature.

Sorbic acid/potassium sorbate:

Used as preservatives to enhance the shelf life of a product.

Therapeutic agents (drugs)

The drugs which have to be incorporated in PLO should satisfy the biological and physicochemical parameters[10].

SKIN STRUCTURE AND BARRIER PROPERTIES

Skin is the most readily accessible organ in the body. Its chief functions are protection, temperature regulation, control of

water output and sensation. The skin of an average body covers a surface area of approximately 2 sq. mts. in most adults, varying in thickness from approximately 1.5 to 4 mm and weighing approximately 2 kg. It receives about one third of the blood that is circulating through the body[11]. Skin consists of the cellular outermost layer, epidermis and relatively a cellular connective tissue matrix dermis as shown in figure:2. Lying between these two layers is a sub- microscopic structure, the basal lamina, which is derived from both the epidermis and the dermis and it serves as an anchoring structure.

The epidermis is composed of two parts: the living cells of the malphygian layer and the dead cells of the horny layer (stratum corneum). Epidermis is composed of 4 cell types; keratinocytes, which constitutes approximately 80% of the epidermis; melanocytes, the source of the melanin pigment; langerhans cells, which are the outmost arm of the immunologic system and serve in host defense; merkel cells, which are thought to function as mechanoreceptors for the sensation. Keratinocytes organize into strata within the epidermis form inside to outside, stratum germinatum, stratum spinosum and stratum corneum.

The stratum corneum typically comprises 10 to 15 cell layers and is approximately 10mm thick when dry. This membrance consisting of dead, anucleate, keratinized cells

embedded in the lipid matrix, is essential for controlling the percutaneous absorption of most drugs and chemicals. The barrier nature of the horny layer depends critically on its constituents, 75-80% proteins, 5-15% lipids and 5-10% unidentified material on a dry weight basis[12]. The protein fraction predominantly comprises of keratin filaments which are cross– linked by inter molecular disulfide bridges[13]. The lipid domain is comprised of an organized distribution of intercellular lamellae derived from intra cellular granules secreted during the epithelial differentiation process[14].

The dermis is 3 to 5 mm thick and is composed of a matrix of connective tissue in which predominant bundles of collagen fibrils interlace with elastic tissue and sparse reticular fibers[12].

Figure.2: Structure of human skin, with potential routes for drug permeation.

Fundamentals of skin permeation.

The sequence of transdermal permeation of the drug is shown in figure:3. The rate of the permeation, dQ/dt across the skin tissues can be expressed mathematically by the following relationship[15].

$$dQ/dt=p_s\,(c_d-c_r)\text{----------}(1)$$

Where c_d and c_r, respectively the concentrations of a skin penetrant in the donor compartment (e.g., the drug concentration at the surface of the stratum corneum) and in the receptor compartment (e.g. Body). P_s is the overall permeability coefficient of the skin tissues to the penetrant as defined by

$$P_s=K_s D_{ss}/h_s$$

Where K_s is the partition – coefficient for the interfacial partitioning of a penetrant molecule form the solution medium or a TDDS on to a stratum corneum; D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues; and h_s is the overall thickness of the skin tissues.

Figure .3: Multilayer skin model showing the sequence of transdermal permeation of drug

Analysis of eq. 1 suggests that to achieve a constant rate of drug permeation one needs to maintain the drug concentration on the surface of stratum corneum (C_d) consistency and substantially greater than the drug concentration in the body (C_r) i.e., $C_d > C_r$; under such a condition eq.1 can be reduced

$$dQ/dt = P_s C_d$$

The rate of skin permeation dQ/dt becomes a constant, if the magnitude of C_d remains fairly constant throughout the course of skin permeation. To maintain C_d at a constant value, it is necessary to make drug release at a rate (R_d) that is either constant or always greater than the rate of skin uptake (R_a) i.e., $R_d > R_a$. By making R_d greater than R_a, the drug concentration on the skin surface (C_d) is maintained at a level equal to or greater than the equilibrium (or saturations) solubility of the drug in the stratum corneum (C_{se}) i.e., $C_d > C_{se}$, and a maximum rate of skin permeation $(dQ/dt)_m$, as expressed by equation (2) is thus achieved.

$$(dQ/dt)_m = P_s C_{se} \text{ ----------(2)}$$

The other mechanism of permeation involves diffusion through shunts particularly those offered by the relatively widely distributed hair follicles and endocrine glands[16]. Typically $1cm^2$ of human skin yields 10 hair follicles, 15 sebaceous glands and 100 sweat glands. However, the appendages provide a small fractional surface area of approximately 0.1% of the total area.

Recent studies[17] indicate the importance of appendages in percutaneous absorption. The appendageal route may be more significant for ions and large polar molecules[18], which slowly permeates through intact stratum corneum. The major fraction of

most diffusants permeates across the bulk of the intact horny layer. The two potential micro pathways serve the stratum corneum through the transcellular and intercellular routes.

The principal pathway taken by the penetrant is decided mainly by diffusants's partition coefficient. Most of the diffusants permeate by both the routes[19]. The intercellular pathway is considered to provide the principal route and the major barrier to the permeation of the most drugs[20,21].

POLYMERS FOR TRANSDERMAL DELIVERY

The polymer controlls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used to a trsnsdermal system.

Drug solubility and diffusibility in the polymer.

The desired drug loading and its effect on polymer integrity.

Compatibility of the polymer with necessary excipients, such as solvents and skin permeation enhancers for the drug.

Skin compatibility: the effect of moisture occluded under the polymer formulation.

Mechanical properties: softness, flexibility, conformability, mechanical integrity.

Ease of fabrication.

Toxicity and purity i.e., compliance with safety requirements of th FDA.

Cost and availability.

Technologies of transdermal delivery system:

Transdermal drug delivery systems are broadly classified into the following three types [24] as shown in figure:4.

I. Reservoir systems. In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied.

II. **Matrix systems, Drug-in-adhesive system.** The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive onto an impervious backing layer. On top of the reservoir, layers of unmedicated adhesive polymer are applied.

Matrix- dispersion system. The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disc is then fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim.

III. Microreservoir systems. This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer *in situ*. Polymers are used in transdermal delivery systems in various ways, including as

1. Matrix formers
2. rate-controlling membranes
3. pressure-sensitive adhesives (PSAs)
4. backing layers
5. Release liners.

1. Matrix formers

The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion–cohesion balance, physicochemical properties, and compatibility and stability with other components of the system as well as with skin[25]**.** A monolithic solid-state design often is preferred for passive transdermal delivery systems because of manufacturing considerations and cosmetic appeal.

1.a. Cross-linked poly (ethylene glycol) (PEG) networks:

Biocompatibility of PEGs make them the polymers of choice. Proteins can be delivered by PEGs cross-linked with tris(6-isocyanatohexyl) isocyanurate by means of a urethane–allophanate bond to obtain polymer networks capable of swelling in phosphate-buffered saline or ethanol and forming gels. These systems have been shown to release the solutes in a biphasic manner.

1.b. Acrylic-acid matrices

Acrylic-acid matrices with plasticizers have been used to make drug–polymer matrix films for TDDS. Some of the polymers that have been reported are Eudragit RL PM, Eudragit S-100, Eudragit RS PM, and Eudragit E-100. Eudragit NE-40D (a copolymer of ethyl acrylate and methyl methacrylate), a

nonadhesive hydrophobic polymer, also has been used as a matrix former.

1.c. Ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) :

The addition of hydrophilic components such as PVP [26] to an insoluble film former such as EC tends to enhance its release-rate constants. This outcome can be attributed to the leaching of the soluble component, which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium. The result is higher dissolution rates. Substances such as PVP act as antinucleating agents that retard the crystallization of a drug.

1.d. Hydroxypropyl methylcellulose (HPMC):

HPMC, a hydrophilic swellable polymer widely used in oral controlled drug delivery, also has been explored as a matrix former in the design of patches of propranolol hydrochloride. HPMC has been shown to yield clear films because of the adequate solubility of the drug in the polymer. Matrices of HPMC without rate-controlling membranes exhibit a bursting effect.

1.e. Organogels:

Some nonionic surfactants such as sorbitane monostearate, lecithin, and Tween tend to associate into reverse micelles. These surfactants in an organic solvent, upon the addition of water, undergo association reorientation to form a

gel. These organogels can be used as a matrix for the transdermal delivery of drugs with greater influx.

2. Rate-controlling membranes

Reservoir-type transdermal drug delivery systems contain an inert membrane enclosing an active agent that diffuses through the membrane at a finite, controllable rate. The release rate–controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid-filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membranes, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the membrane thickness.

2.a. EVA:

EVA frequently is used to prepare rate-controlling membranes in TDDS because it allows the membrane permeability to be altered by adjusting the vinyl acetate content of the polymer. When ethylene is copolymerized with vinyl acetate, the degree of crystallinity and the crystalline melting point decreases and amorphousness increases.. An increase in Tg reflects a decrease in the polymer-chain mobility and hence the solute diffusivity[27].

2.b. Silicone rubber:

The silicone rubber group of polymers has been used in many controlled-release devices. These polymers have an outstanding combination of biocompatibility, ease of fabrication, and high permeability to many important classes of drugs, particularly steroids.

2.c. Polyurethane:

Polyurethane is the general term used for a polymer derived from condensation of polyisocyanates and polyols having an intramolecular urethane bond or carbamate ester bonds (-NHCOO-). Although most polyurethanes presently used are of the polyether type because of their high resistance to hydrolysis, polyester polyurethanes recently have become the focus of attention because of their biodegradability.

3. PSAs:

A PSA is a material that adheres with no more than applied finger pressure, is aggressively and permanently tacky, exerts a strong holding force, and should be removable from a smooth surface without leaving a residue. The general formula for a PSA includes an elastomeric polymer, a tackifying resin, a necessary filler, various antioxidants, stabilizers if required, and cross-linking agents. When formulating a PSA, a balance of four properties must be taken into account: tack, peel adhesion, skin adhesion, and cohesive strength.

3.a. Polyisobutylene (PIB):

Isobutylene polymerizes in a regular head-to-tail sequence by low-temperature cationic polymerization to produce a polymer having no asymmetric carbons. In its unstrained state, the polymer is in an amorphous state, and the Tg of the polymer is ~-70 °C. The physical properties of the polymer change gradually with increasing molecular weight.

3.b. Polyacrylates:

Acrylic esters are represented by the general formula CH2=CH-COOR. The nature of the R group determines the properties of each ester and the polymer it forms. Polymers of this class are amorphous and are distinguished by their water-clear color in solution and stability toward aging. As is typical of polymer systems, the mechanical properties of acrylic polymers improve as the molecular weight increases.

3.c. Silicones:

Silicone PSAs comprise polymer or gum and a tackifying resin. The adhesive is prepared by cross linking the reactants in solution by a condensation reaction. Unlike acrylic-, rubber-, and PIB-based adhesives, medical-grade silicone adhesives do not contain organic tackifiers, stabilizers, antioxidants, plasticizers, catalysts, or other potentially toxic extractables.

3.d. Hot-melt PSAs (HMPSAs):

When HMPSAs are heated, they melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flowless state. HMPSAs are advantageous over solvent-based systems because they

- do not require removal and containment of the solvents.
- do not require special precautions to avoid fire.
- are amenable to coating procedures other than those commonly used with solvent-based systems.
- are more easily coated into full thickness with minimal bubbling, which often results with solvent-containing PSAs.

4. Backing layer

When designing a backing layer, the developer must give chemical resistance of the material foremost importance. Excipient compatibility also must be seriously considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug, or penetration enhancer through the layer. The most comfortable backing may be the one that exhibits the lowest modulus or high flexibility, good oxygen transmission, and a high moisture-vapor transmission rate. In a novel modification to the conventional design, a patch was fabricated in which the backing itself acted

as a reservoir for the drug. The upper internal portion of the drug reservoir infiltrated the porous backing and became solidified therein after being applied so that the reservoir and the backing were unified. This modification enabled the backing itself to act as a storage location for the medication-containing reservoir [28].

5. Release liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to the skin. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form delivering the active principle.

However, because the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding the chemical inertness and permeation to the drug, penetration enhancer, and water. In case cross-linking is induced between the adhesive and the release liner, the force required to remove the liner will be unacceptably high [29,30].

Figure .4: Representative designs of transdermal drug delivery systems.

Table.1: Characteristics of some commercially available backing materials:

Table: 2. Examples of marketed TDDS

ADVANTAGES AND LIMITATIONS OF T.D.D.S

Advantages of TDDS:

- Avoids vagaries associated with gastro- intestinal absorption due to pH, enzymatic activity, and food interactions.
- It is substitute for oral route.
- Avoids first pass effect (drug deactivation by digestive and liver enzymes)
- It avoids the risks and inconveniences of IV therapy.
- Provides predictable extended duration of activity.
- Extends the activity of drugs with short half lives.
- Multi day therapy with single application.
- Provides capacity to terminate drug effects rapidly.
- Rapid identification of medication in emergency eg., unconscious coma patients.
- Minimize inter and intra patient variation.
- Reduces daily dosing, thus improving patient compliance.

Limitations of TDDS:

- Limited time that the patch can remain affixed.
- Variable intra and inter individual percutaneous absorption efficiency.
- Skin rashes and sensitization.
- Bacterial and enzymatic drug metabolism under the patch.
- Complex technology / high cost.

SELECTION OF THERAPEUTIC DRUG CANDIDATES FOR TRANSDERMAL DELIVERY:

The choice of drugs to be delivered is almost a difficult one and careful considerations should be given for the selection of suitable drug molecule. The following are some of the desirable properties of a drug for TDDS [31].

Physico– chemical properties of drug:

- The drug should have a molecular weight of less than 750.
- The drug should possess balanced lipophilic hydrophilic characteristics and also have reasonable solubility in both lipid and aqueous phases.
- The log P value should be in the range 1-3.
- The melting point should be less than 200°C.
- Saturated aqueous solution of the drug should have pH value between 5 and 9.

Biological properties of drug:

- The biological half life ($t_{1/2}$) should be less than 5-6 hours.
- The drug should be potent with a daily systemic dose of less than 20 mg.
- The drug should not stimulate an immune reaction in the skin.
- The drug must not induce a cutaneous irritant or allergic response.

Finally in order to obtain the best candidate for transdermal drug delivery, an attempt should be made to keep the melting point as low as possible. Obviously, in some cases, there will be a compromise between optimizing both the partition and solubility parameters and incorporation of a suitable penetration enhancer[32, 33,34,35].

PENETRATION ENHANCER:

Penetration enhancers are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin.[36, 37, 38.]

The properties of ideal penetration enhancers are:

- Pharmacologically inert.
- Non toxic, non irritating & non allergic
- Rapid onset of action, predictable and suitable duration of action for drug used.
- Readily incorporated into the delivery system.
- Following removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property.
- Chemically and physically compatible with the delivery system.
- Commonly used Chemical enhancers are Sulfoxides and Similar Compounds [39,40].

Pyrrolidones

Pyrrolidones have great potential to be used as transdermal permeation enhancers. The most common *N*-methyl-2-pyrrolidone (NMP) has been used widely to enhance the skin absorption of many drugs, (insulin, ibuprofen, and flurbiprofen). The flux of the anti-inflammatory drug ibuprofen increased 16 times. Eg. Azone.

Fatty acids and esters

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. An increase of 6.5-17.5-fold in the permeation rate of flurbiprofen was studied. They have a greater enhancing effect on lipophilic drugs. Eg. Oleic acid.

Sulfoxides and similar compounds

DMSO, the most important compound belonging to the category of sulfoxides and similar compounds, enhances the transdermal permeation of a variety of drugs, like β-blockers, ephedrine HCL, and papaverine hydrochloride. It also enhances the release of azapropazone from its ointments .eg. Decylmethyl sulfoxide (DCMS).

Alcohols, glycols, and glycerides

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. It increases the permeation of ketoprofen from a gel-spray formulation and triethanolamine salicylate from a hydrophilic emulsion base. It also acts as a vehicle for menthol in increasing the penetration of methyl paraben. eg glycerin tricaprylate, Lauryl alcohol.

Cyclodextrin complexes

Cyclodextrin complexes of a number of drugs have been formed, and such a combination usually enhances the permeation of drugs. For instance, an inclusion complex of piroxicam with β-cyclodextrin increased the drug flux three times across hairless mouse skin.

Amino acid derivatives

Various amino acid derivatives have been investigated for their potential in improving percutaneous permeation of drugs. *N*-Dodecyl-l-amino acid methyl ester and *N*-pentyl- *N*-acetyl prolinate were studied. Application of these two enhancers on excised hairless mouse skin 1 hr prior to drug treatment produced greater penetration of hydrocortisone from its suspension.

Clofibric acid

Esters and amides of clofibric acid were studied for their permeation-enhancing property using nude mice skin. The best enhancement of hydrocortisone-21 acetate and betamethasone-17-valerate was observed with clofibric acid octyl amide when applied 1 hr prior to each steroid.

Dodecyl-*N*,*N*-dimethylamino acetate

DDAA increased the transdermal permeation of a number of drugs, like propranolol hydrochloride and timolol maleate. It was found to be as effective an enhancer as azone, but it possesses an advantage over azone: Skin irritation with DDAA is reversed in a short time compared to azone[41].

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

Currently, tremendous research is going on in the evaluation of T.D.D.S. The objective of this research is often to find correlation between laboratory results *(In-vitro*) and the transdermal absorption experienced by living subjects, so that *in-vivo* experimentation may be curtailed. There is a definite need for the development and implementation of a single, probably universal, dissolution method to assure patch – to– patch uniform release. The aim of *in-vitro* experimentation in TDDS is to understand and/ or predict the delivery and penetration of a molecule form the skin surface into the body.

TDDS can be described in three principal stages for understanding in designing of suitable *in-vitro* experiment[42.43]

- Delivery of the molecules to the skin Surface
- Passage of the molecule through the skin
- Delivery of the molecule into the body *in- vivo* = recovery of the molecule *in-vitro*[44].

DIABETES MELLITUS AND ITS TREATMENT [45,46.]

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration-hyperglycaemia (fasting plasma glucose > 7.0 mmol/l, or plasma glucose > 11.1 mmol/l 2 hours after a meal)-caused by insulin deficiency, often combined with insulin resistance. Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which in turn, results in dehydration, thirst and increased drinking (polydipsia).

Insulin deficiency causes increased breakdown and reduced synthesis of proteins. *Diabetic ketoacidosis* is an acute emergency. It develops in the absence of insulin because of accelerated breakdown of fat to acetyl-CoA, which, in the absence of aerobic carbohydrate metabolism, is converted to acetoacetate and β-hydroxybutyrate (which cause acidosis) and

acetone (a ketone). Although insulin treatment has greatly increased the life expectancy of the diabetic patient, diabetes remains the third leading cause of death by disease, the second leading cause of blindness, and the second leading cause of renal failure.

CONTROL OF BLOOD GLUCOSE

Glucose is the obligatory source of energy for the brain, and physiological control of blood glucose reflects the need to maintain adequate fuel supplies in the form of intermittent food intake and variable metabolic demands. More fuel is made available by feeding than is immediately required and excess calories are stored as glycogen or fat. During fasting, these energy stores need to be mobilized in a regulated manner. The most important regulatory hormone is insulin.

Increased blood sugar stimulates insulin secretion, whereas reduced blood sugar reduces insulin secretion. Hypoglycemia, caused by excessive insulin, not only reduces insulin secretion but also elicits secretion of an array of 'counter-regulatory' hormones, including *glucagon*, *adrenaline*, *glucocorticoids* and *growth hormone*, all of which increase blood glucose.

CLINICAL MANAGEMENT OF DIABETES

Diet is the cornerstone of the management of diabetes, regardless of the severity of the symptoms or the type of diabetes. Exercise is also an important component in managing

diabetes, particularly in obese individuals with NIDDM who may have a component of insulin resistance as a consequence of obesity. Treatment regimens that have proved effective include a calorie restricted diet in combination with exogenous insulin or oral hypoglycemic drugs. However, since diet, exercise, and oral hypoglycemic drugs, often because of noncompliance by the patient, will not always achieve the clinical objectives of controlling the symptoms of diabetes, insulin remains universally important in therapeutic management.

The administration of insulin is required for the treatment of Type I (IDDM) and in cases of Type II (NIDDM) that are refractory to management with oral hypoglycemic drugs. Because the spectrum of patients with diabetes extends from the totally asymptomatic individual to one with life-threatening ketoacidosis, therapeutic management must be highly individualized. An important objective is to maintain a Glucose level as close to normal as possible without producing frequent hypoglycemia or overly restricting the patient's lifestyle. Many diabetics aim to achieve an average blood glucose below 150 (hemoglobin A1c < 7%). Unstable or ketoacidosisprone diabetics are difficult to maintain with a single dose of either intermediate- or long-acting insulin; they usually require multiple injections of combinations of short-, intermediate-, and/or long-acting insulin preparations.

For the purpose of rational management, it is appropriate to classify diabetes as the following.

- Type 1 diabetes.
- Type 2 diabetes.

Type 1 diabetic patients are usually young (children or adolescents) and not obese when they first develop symptoms. There is an inherited predisposition, with a 10-fold increased incidence in first-degree relative of an index case, and strong associations with particular histocompatibility antigens (HLA types). Studies of identical twins have shown that genetically predisposed individuals must additionally be exposed to an environmental factor such as viral infection (e.g. with coxsackievirus or echovirus). Viral infection may damage pancreatic B cells and expose antigens that initiate a self-perpetuating autoimmune process. The patient becomes overtly diabetic only when more than 90% of the β cells have been destroyed.

Type 2 diabetes is accompanied both by insulin resistance (which precedes overt disease) and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as β-cell function declines. Treatment is initially dietary, although oral hypoglycemic drugs usually become necessary, and about one-third of patients ultimately require insulin. Prospective studies

have demonstrated a relentless deterioration in diabetic control over the years.

Table:3. DIFFERENCE BETWEEN TYPE 1 AND TYPE 2 DIABETES [47]

Characteristics	Type 1	Type 2
Other names	Previously : insulin-dependent diabetes mellitus (IDDM) : juvenile-onset diabetes mellitus	Previously : non-insulin-dependent diabetes mellitus (NIDDM): adult onset diabetes mellitus
Diabetic population	5-10%	90%
Age of onset	Usually < 30 year, peaks at 12-14 yr, rare before 6 months, some adults develop type 1 during the fifth decade	Usually > 40 year, but increasing prevalence among obese children.
Pancreatic function	Usually none, although some residual C-peptide can sometimes be detected at diagnosis, especially in adults	Insulin present in low, normal, or high amounts

Pathogenesis	Associated with certain HLA types; presence of islet cell antibodies suggests autoimmune process	Defect in insulin secretion, tissue resistance to insulin; ↑ hepatic glucose output.
Family history	Generally not strong	Strong
Obesity	Uncommon unless "overinsulinized" with exogenous insulin	Common (60-90%)
Ketoacidosis history	Often present	Rare, except in circumstances of unusual stress (eg.infection)
Clinical presentation	Moderate to severe symptoms (polyuria, polydipsia, fatigue, weight loss, ketoacidosis)	Mild polyuria, fatigue, often diagnosed on routine physical or dental examination
Treatment	Insulin, diet, exercise	Diet, exercise, insulin, anti diabetic agents

Other specific types of diabetes are :

- Genetic defects of β-cell function (eg.MODY).
- Diseases of the endocrine pancreas.
- Endocrinopathies
- Drug or chemical induced.
- Infections.
- Gestational Diabetes Mellitus (GDM) .

SULFONYL UREAS[48,49,50]

They lower blood glucose level in normal subject*s* and in type 2 diabetics, but not in type 1 diabetics.

MECHANISM OF ACTION:

A. Insulin release from pancreatic β- cells

Sulfonylureas bind to a 140-kDa high-affinity sulfonylurea receptor that is associated with a β-cell inward rectifier ATP-sensitive potassium channel. Binding of a sulfonylurea inhibits the efflux of potassium ions through the channel and results in depolarization. Depolarization opens a voltage-gated calcium channel and results in calcium influx and the release of preformed insulin.

B. Reduction of serum glucagon concentrations

Long-term administration of sulfonylureas to type 2 diabetics reduces serum glucagon levels, which may contribute to the hypoglycemic effect of the drugs. The mechanism for this suppressive effect of sulfonylureas on glucagon levels is unclear but

appears to involve indirect inhibition due to enhanced release of both insulin and somatostatin, which inhibit A-cell secretion.

C. Potassium channel closure in extrapancreatic tissues

Insulin secretagogues bind to sulfonylurea receptors in potassium channels in extrapancreatic tissues, but the binding affinity varies among the drug classes and is much less avid than for the β-cell receptors. The clinical significance of extrapancreatic binding is not known. A minor action reducing glucagon and increasing somatostatin release has been demonstrated. Hepatic degradation of insulin may be slowed.

PHARMACOKINETIC ASPECTS

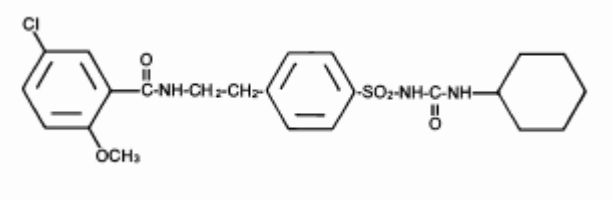
Sulfonylureas are well absorbed after oral administration, and most reach peak plasma concentrations within 2-4 hours. The duration of action varies. All bind strongly to plasma albumin and are implicated in interactions with other drugs (e.g. salicylates and sulfonamides) that compete for these binding sites. Most sulfonylureas (or their active metabolites) are excreted in the urine, so their action is increased in the elderly and in patients with renal disease. Most sulfonylureas cross the placenta and enter breast milk.

Sulfonylureas require functional β cells, so they are useful in the early stages of type 2 diabetes. They can be combined with metformin or with thiazolidinediones.

DRUG AND POLYMER PROFILE

GLYBURIDE [51,52,53,54]

Chemical structure



Chemical Formula: $C_{23}H_{28}ClN_3O_5S$

Chemical IUPAC Name:

5-chloro-N-[2- [4-(cyclohexylcarbamoylsulfamoyl) phenyl] ethyl] -2-methoxybenzamide.

DESCRIPTION

GLYBURIDE, also known as **GLIBENCLAMIDE**, is an anti-diabetic drug in a class of medications known as sulfonylureas.

Synonyms

Apo-Glibenclamide

Glibenclamida [INN-Spanish]

Glibenclamidum [INN-Latin]

Glibenclamide

Brand Mixtures

Glucovance (Metformin + GLYBURIDE)

Average Molecular Weight : 494.0040

State : Solid (odorless, white,

crystalline compound)

Melting Point : 169-170°C

Solubility **:** Solubility of the drug in water is approximately 4 μg/ml at pH 4 and 600 μg/ml at pH 9 and 3 mg/ml in alcohol.

LogP : 3.78

DOSAGE

Daily dose **:** 5 – 15 mg

Initial **:** 2.5-5 mg/day, administered with breakfast or with the first main meal of the day. In patients who are more sensitive to hypoglycemic drugs, start at 1.25 mg/day. Increase in increments of no more than 2.5 mg/day at weekly intervals based on the patient's blood glucose response .

Maintenance : 1.25-20 mg/day given as single or divided doses.

Elderly : Initial: 1.25-2.5 mg/day, increase by 1.25-2.5 mg/day every 1-3 weeks.

Transfer From Other Hypoglycemic Therapy Patients Receiving Other Oral Antidiabetic Therapy

Transfer of patients from other oral antidiabetic regimens to glyburide should be done conservatively and the initial daily dose should be 2.5 to 5 mg.

Patients Receiving Insulin

Some Type II diabetic patients being treated with insulin may respond satisfactorily to glyburide. If the insulin dose is less than 20 units daily, substitution of glyburide tablets 2.5 to 5 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on glyburide tablets 5 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to glyburide. In these patients, insulin dosage is decreased by 50% and glyburide tablets 5 mg daily is started.

How to use: Take this medication by mouth with breakfast or with the first main meal.

No of doses per day: 1 -2 (usually once daily; or use as directed by the doctor. Some patients, especially those taking higher doses, may be directed to take this drug twice a day. The dosage is based on the medical condition and response to therapy).

MISSED DOSE: If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule.

Maximum Dose

Daily doses of more than 20 mg are not recommended.

Reference Range:

Target range	Adults
Fasting blood glucose	<120 mg/dL
Glycosylated hemoglobin	<7%

Drug Category

Antiarrhythmic Agents.

Hypoglycemic Agents.

Sulfonylureas.

Alternative to insulin in women for the treatment of gestational diabetes (11-33 weeks gestation).

Indication

Indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone. Glyburide, is approximately 150 times as potent as tolbutamide on a molar basis and twice as potent as Glipizide.

Pharmacology

Glyburide (INN), also known as glibenclamide (USAN), a second-generation sulfonylurea antidiabetic agent, appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonyl-urea hypoglycemic drugs. The combination of glyburide and metformin may have a synergistic effect. In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by

enhancement of renal free water clearance. Glyburide is twice as potent as the related second-generation agent glipizide.

Mechanism of Action

Sulfonylureas such as glyburide likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin.

Absorption

Significant absorption within 1 hour and peak plasma levels are reached within 4 hours and low but detectable levels at twenty-four hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose.

Toxicity **:** Oral rat LD_{50}: > 20,000 mg/kg.
Oral mouse LD_{50}: 3250 mg/kg.

Protein Binding : >99% Extensively bound to serum proteins

Biotransformation

Primarily hepatic (mainly cytochrome P450 3A4). The major metabolite is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites contribute no significant hypoglycemic action in humans as they are only weakly active.

Half-life elimination : 5-16 hours; may be prolonged with renal or hepatic impairment.

Time to peak, serum : Adults: 2-4 hours.

Clearance route : Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Dosage Forms **:** tablets, micronized tablets

Food Interactions

Avoid alcohol.

Avoid sugar and sugary food.

Take 30-60 minutes before breakfast.

Remarks: Potent but slow acting, marked initial insulinemic action, may work when others fail, metabolite excreted in urine as well as in bile, single daily dose possible despite short $t_{1/2.}$

Adverse effects

can cause hypoglycemia (which stimulates appetite and leads to weight gain).

are effective only if β-cells are functional.

block ATP-sensitive potassium channels in β-cells.

are well tolerated but promote weight gain.

Contraindications

Glyburide are contraindicated in patients with:

Known hypersensitivity or allergy to the drug.

Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

Storage: Store at room temperature away from light and moisture.

POLYMER PROFILE[55]

POLYVINYL ALCOHOL

Nonproprietary Names

PhEur : Poly(vinylis acetas)

USP : Polyvinyl alcohol

Synonyms

Airvol; Alcotex; Elvanol; Gelvatol; Gohsenol; Lemol; Mowiol; Polyvinol; PVA; vinyl alcohol polymer.

Chemical Name and CAS Registry Number

Ethenol, homopolymer [9002-89-5]

Empirical Formula and Molecular Weight

PVA is a water-soluble synthetic polymer represented by the formula $(C2H4O)_n$. The value of n for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20000–200000.

Functional Category

Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

PVA is used primarily in topical pharmaceutical and ophthalmic formulations; It is used as a stabilizing agent for emulsions (0.25–3.0% w/v). PVA is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration, and in transdermal patches. PVA may be made into microspheres when mixed with a glutaraldehyde solution.

Description

PVA occurs as an odorless, white to cream-colored granular powder.

Pharmacopeial Specifications

TYPICAL PROPERTIES

Melting point:

2288°C for fully hydrolyzed grades;

180–1908°C for partially hydrolyzed grades.

Refractive index : $n^{25}_{D} = 1.49–1.53$

Solubility : Soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents. Dissolution requires dispersion (wetting) of the solid in water at room temperature followed by

heating the mixture to about 908°C for approximately 5 minutes. Mixing should be continued while the heated solution is cooled to room temperature.

Specific gravity:

1.19–1.31 for solid at 258°C;

1.02 for 10% w/v aqueous solution at 258°C.

Specific heat: 1.67 J/g (0.4 cal/g)

Stability and Storage Conditions

PVA is stable when stored in a tightly sealed container in a cool, dry place. Aqueous solutions are stable in corrosion-resistant sealed containers. Preservatives may be added to the solution if extended storage is required. PVA undergoes slow degradation at 1008°C and rapid degradation at 2008°C; it is stable on exposure to light.

Incompatibilities

PVA undergoes reactions typical of a compound with secondary hydroxy groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of PVA 5% w/v can be caused by phosphates. Gelling of PVA solution may occur if borax is present.

Safety

PVA is generally considered as a nontoxic material. It is nonirritant to the skin and eyes at concentrations up to 10%; concentrations up to 7% are used in cosmetics. Studies in rats have shown that PVA 5% w/v aqueous solution injected subcutaneously can cause anemia and infiltrate various organs and tissues

LD50 (mouse, oral): 14.7 g/kg
LD50 (rat, oral) : >20 g/kg

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. PVA dust may be an irritant on inhalation. Handle in a well-ventilated environment.

POVIDONE

Nonproprietary Names

BP : Povidone

JP : Povidone

PhEur : Povidonum

USP : Povidone

Synonyms

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight

The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, in the range 10–120. The K-value is calculated using Fikentscher's equation.

Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation or Technology

Although PVP is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions.

Description

PVP occurs as a fine, white to creamy-white colored odorless or almost odorless, hygroscopic powder. PVP with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Pharmacopeial Specifications

TYPICAL PROPERTIES

Acidity/alkalinity : pH = 3.0–7.0 (5% w/v aqueous solution).

Density (bulk) : 0.29–0.39 g/cm^3 for Plasdone.

Density (tapped) : 0.39–0.54 g/cm^3 for Plasdone.

Density (true) : 1.180 g/cm^3

Flowability : 20 g/s for povidone K-15;
16 g/s for povidone K-29/32.

Melting point : softens at 1508°C.

Moisture content : povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Particle size distribution:

Kollidon 25/30: 90% >50 mm, 50% >100 mm, 5% >200 mm;
Kollidon 90: 90% >200 mm, 95% >250 mm.

Solubility : Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a

solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic): The viscosity of aqueous PVP solutions depends on both the concentration and the molecular weight of the polymer employed.

Stability and Storage Conditions

PVP darkens to some extent on heating at 1508°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–1308°C; steam sterilization of an aqueous solution does not alter its properties.

Incompatibilities

PVP is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thiomerosal, may be adversely affected by the formation of complexes with PVP.

Safety

PVP has been used in pharmaceutical formulations for many years, being first used in the 1940's as a plasma expander, although it has now been superseded for this purpose by dextran. PVP is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, PVP may be regarded as essentially

nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

HYPROMELLOSE

Nonproprietary Names

BP : Hypromellose

JP : Hydroxypropylmethylcellulose

PhEu : Hypromellosum

USP : Hypromellose

Synonyms : Benecel MHPC; hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; pharmacoat; spectracel 6; spectracel 15; tylopur.

Chemical name and CAS registry number

Cellulose, 2-hydroxypropyl-methyl ether [9004-65-3].

Empirical formula molecular weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2- hydroxypropylated) cellulose. It is available in

several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2 % w/w aqueous solution at 20°C. Hypromellose defined in the USP 25 specifies the substitution type by appending a four- digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxy propoxy group (OCH_2CH (OH) CH_3), calculated on a dried basis. Molecular weight is approximately 10,000 – 1500,000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Functional category

Coating agent; film former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

Applications in pharmaceutical formulations or technology

HPMC is widely used in oral and topical pharmaceuticals, particularly ophthalmic preparations. Compared with methylcellulose, HPMC produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use.

Description

HPMC is an odorless and tasteless, white or creamy white fibrous or granular powder.

Pharmacopeial specifications

TYPICAL PROPERTIES

Acidity / alkalinity	**:**	pH=5.5 – 8.0 for a 1% w/w aqueous Solution.
Ash	:	1.5 – 3.0% depending upon the grade
Autoignation temperature	:	360°C
Density (tapped)	:	0.557 g/cm^3
Density (untapped)	:	1.326 g/cm^3
Melting point	:	browns at 190 - 200°C ; Chars at 225 - 230°C.

Glass transition temperature is 170 - 180°C

Moisture content : HPMC absorbs moisture from the atmosphere; the amount of water absorbed depends on the relative humidity of the surrounding air.

Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity **:** 1.26

Viscosity (dynamic) **:** wide ranges of viscosity types are commercially available.

Stability and storage conditions:

HPMC powder is a stable material, although, it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. HPMC undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 80-90°C, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme-resistent, providing good viscosity stability during long-term storage.

Incompatibilities

HPMC is incompatible with some oxidizing agents. Since it is nonionic, HPMC will not complex with metallic salts or ionic organics form insoluble precipitates.

Safety

HPMC is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. HPMC is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an accepatable daily intake of HPMC since the levels consumed were not considered to represent a hazard to health.

LD_{50}(mouse, IP): 5 g /kg

LD_{50}(rat, IP) : 5.2 g /kg

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. HPMC dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. HPMC is combustible.

ETHYLCELLULOSE

Nonproprietary Names

BP	:	Ethylcellulose
PhEur	:	Ethylcellulosum
USPNF	:	Ethylcellulose

Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name and CAS registry number

Cellulose ethyl ether [9004-57-3].

Functional category

Coating agent; suspending agent; tablet binder; thickening agent; viscosity – increasing agent.

Applications in pharmaceutical formulation or technology

EC is widely used in oral and topical pharmaceutical formulations. The main use of EC in oral formulations is as a

hydrophobic coating agent for tablets and granules. EC coatings are used to modify the release to a drug to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with EC to inhibit oxidation. Modified – release tablet formulations may also be produced using EC as a matrix former.

Description

EC is a tasteless, free-flowing, white or light tan-colored powder.

Pharmacopeial specifications

TYPICAL PROPERTIES

Density (bulk) : 0.4 g/cm^3

Glass transition temperature : 129-133℃

Moisture content

EC absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility

EC is practically insoluble in glycerin, propylene glycol, and water. EC that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). EC that contains not less than 46.5% of ethoxyl acetate, methanol, and toluene.

Specific gravity : 1.12 - 1.15 g/cm^3

Viscosity

The viscosity of EC is measured typically at 25°C using 5% w/v EC dissolved in a solvent blend of 80% toluene : 20% ethanol (w/w). Grades of EC with various viscosities are commercially available. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPas (7-100 cp). Specific EC grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

Stability and storage conditions

EC is a stable, slightly hygroscopic material. It is chemically resistant to alkalies, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Safety

EC is widely used in oral and topical pharmaceutical formulations. It is also used in food products. EC is not metabolized following oral consumption and is therefore a noncalorific

substance. Because EC is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

EC is generally regarded to be a health hazard; the WHO has not specified an acceptable daily intake.

LD_{50} (rabbit, skin): >5 g/kg

LD_{50} (rat, oral) : >5 g/kg

Handling precautions

It is important to prevent fine dust clouds of EC from reaching potentially explosive levels in the air. EC is combustible. EC powder may be an irritant to the eyes and eye protection should be worn.

POLOXAMER

Nonproprietary Names

BP : Poloxamers

PhEur : Poloxamera

USPNF : Poloxamer

Synonyms

Lutrol; Monolan; Pluronic; poloxalkol; polyethylene–propylene glycol copolymer; polyoxyethylene–polyoxypropylene copolymer; Supronic; Synperonic.

Chemical Name and CAS Registry Number

a-Hydro-o-hydroxypoly(oxyethylene)poly(oxypropylene) poly (oxyethylene) block copolymer [9003-11-6]

Empirical Formula and Molecular Weight

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula $HO(C2H4O)_a(C3H6O)_b(C2H4O)_aH$. The PhEur 2005 states that a suitable antioxidant may be added.

Functional Category

Dispersing agent; emulsifying and coemulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

Applications in Pharmaceutical Formulation or Technology

Poloxamers are nonionic polyoxyethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range.

Description

Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

Pharmacopeial Specifications

TYPICAL PROPERTIES

Acidity/alkalinity: pH = 5.0–7.4 for a 2.5% w/v aqueous

solution.

Cloud point : >1008°C for a 1% w/v aqueous solution, and a 10% w/v aqueous solution of poloxamer 188.

Density : 1.06 g/cm3 at 258°C

Flash point : 2608°C

Flowability : solid poloxamers are free flowing.

HLB value : 0.5–30; 29 for poloxamer 188.

Melting point :

168°C for poloxamer 124;

52–578°C for poloxamer 188;

498°C for poloxamer 237;

578°C for poloxamer 338;

52–578°C for poloxamer 407.

Moisture content : poloxamers generally contain less than 0.5% w/w water and are hygroscopic only at relative humidity greater than 80%.

Solubility: solubility varies according to the poloxamer type.

Surface tension :

19.8mN/m (19.8 dynes/cm) for a 0.1% w/v aqueous poloxamer 188 solution at 258°C;

24.0mN/m (24.0 dynes/cm) for a 0.01% w/v aqueous poloxamer 188 solution at 258°C;

26.0mN/m (26.0 dynes/cm) for a 0.001% w/v aqueous poloxamer solution at 258°C.

Viscosity (dynamic): 1000 mPa s (1000 cP) as a melt at 778°C for poloxamer 188.

Stability and Storage Conditions

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mold growth. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens.

Safety

Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials.

Acute animal toxicity data for poloxamer 188

LD50 (mouse, IV): 1 g/kg,

LD50 (mouse, oral): 15 g/kg,

LD50 (mouse, SC): 5.5 g/kg,

LD50 (rat, IV): 7.5 g/kg,

LD50 (rat, oral): 9.4 g/kg.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

REVIEW OF LITERATURE

Veena S Belgamwar[10] *et.al.,* Gives a detail insight of pluronic lecithin organogels (PLOs) as a topical and transdermal drug delivery system. PLO is a microemulsion-based gel that has been effectively used by physicians and pharmacists to deliver hydrophilic and lipophilic drugs topically and transdermally across the stratum corneum. Various types of therapeutic agents have been easily incorporated in PLO to improve their topical drug delivery. Beside this, it shows low skin irritation, increases patient compliance, reduces side effects, avoids first pass metabolism, and increases efficiency of drug. In addition, PLO has been shown *in vivo* and *in vitro* to modulate the release and permeation of drugs applied transdermally.

Shaila Lewis[55] *et.al*.**,** developed transdermal patches of nicotine, which are cost effective and conducive to the Indian market. Two types of patches, monolayered and bilayered, were prepared. The monolayered patch bore a rate- controlling membrane, whereas the bilayered, served as matrix type. The physical characteristics of the patches were evaluated by standard techniques. The drug content was found to be uniform in the patches. *In vitro* release studies of transdermal patches showed a biphasic release pattern, with diffusion as the dominating mechanism of drug release for the matrix type, while the membrane-controlled release nicotine, gradually over the 24 h study.

Sanap G.S[56] *et.al.,* formulated transdermal drug delivery systems of indapamide by using solvent casting method. Monolithic systems were prepared by HPMC and EC polymers by incorporating glycerine and dibutyl phthalate as plasticizers, respectively. The *in vitro* drug release studies indicated that HPMC containing films have shown better release than that of EC containing films without any permeation enhancer. The various permeation parameters such as flux, permeability coefficient, enhancement ratio and diffusion rate constants were determined for all the formulations. The maximum flux of 9.08 x 10^{2} mg/cm^{2} h was observed with HPMC monolithic system containing 30% w/w olive oil. A significant improvement of flux was observed in the following order: olive oil> linseed oil > sunflower oil > cottonseed oil > coconut oil > castor oil. The *in vitro* release studies revealed that the release was sustained up to 24 h and it follows zero-order kinetics.

Jianping Wang[57] *et.al*.**,** prepared Sinomenine transdermal patch by salivation method using PVA and PVP and its properties were studied. The releasing rate *in vitro* of the patch was determined by HPLC. Peel test was used to evaluate the adhesion. Acute skin irritation test was performed in comparison with formalin (0.8%) by using mouse model. The Sinomenine TDDS Patch was prepared. The releasing rate *in vitro* followed the Higuchi equation (r^2 >0.99), the releasing amount was beyond 90% in 24h. The peel adhesion to steel (N/25 mm) is 10 or above. The skin irritation tests showed negligible erythema and edema. The Sinomenine transdermal patch was prepared successfully and it may be beneficial for topical use.

Biswajit Mukherjee[58] *et.al.,* Prepared transdermal matrix patches containing the drug, diclofenac diethylamine with various polymeric combinations of PVP and EC and to study the mechanism of release of the drug from the patches and its skin permeation. Sorbitan monolaurate 20 (Span 20), a non-ionic surfactant was added to the concentrations (0.1% wt/vol), as a skin permeation enhancer. *In vitro* skin permeation studies, with rat skin, using a modified Keshary-Chien diffusion cell, were carried out. There was about a 29% to 30% enhancement of skin permeation of the drug using Span 20 and the formulation with PVP: EC 3:5 shows high skin permeation.

Yuveraj Singh Tanwar[59] *et.al*., formulated transdermal patches of carvedilol with a HPMC-drug reservoir by the solvent evaporation technique. In this investigation, the membranes of Eudragit RL100 and Eudragit RS100 were cast to achieve controlled release of the drug. The prepared patches possessed satisfactory physicochemical characteristics. *In vitro* permeation studies were performed using a K-C diffusion cell across hairless guinea pig skin and followed the super case II transport mechanism. The effects of non-ionic surfactants Tween 80 and Span 80 on drug permeation were studied. The non- ionic surfactants in the patches increased the permeation rate, Span 80 exhibiting better enhancement relative to Tween 80. Transdermal patches consisting of the HPMC-drug reservoir with Span 80 as permeation enhancer and rate-controlling membranes of Eudragit RS100 and Eudragit RL100 demonstrated sustained and controlled release of the drug.

Bagyalakshmi J[60] *et.al.,* Developed ampicillin sodium transdermal patch against *Escherichia coli*. The efficiency of ampicillin sodium against *E. coli* was investigated in an *in vitro* infection model which simulates human pharmacokinetics. The *E. coli* stains were exposed to transdermal patch with different kinds of polymers such as sodium alginate, cellulose acetate phthalate, HPMC, chitosan and CMC and the drug releasing capacity was studied through colony-forming units (CFU). The process was carried out for 24 h at 37°C. It was found out that HPMC was the best polymer that gave less number of CFU, followed by CMC, chitosan, CAP and sodium alginate.

Sriniva Mutalik[61] *et.al.,* developed the membrane controlled transdermal systems of glibenclamide and to evaluate with respect to various *in vitro* and *in vivo* parameters. The membrane moderated transdermal systems were prepared using drug containing carbopol gel as reservoir and EC, Eudragit RS-100, Eudragit RL-100 and Ethylene vinyl acetate (EVA) rate controlling membranes. The possible interaction between drug and polymer was studied by IR spectroscopy, DSC and HPTLC analysis. The hypoglycemic activity of the systems was studied in both normal and diabetic mice. Various biochemical parameters and histopathological studies were carried out. The system with EVA rate controlling membrane was selected for in vivo experiments. The transdermal system produced better improvement with respect to hypoglycemic activity, glucose tolerance test, and exhibited negligible skin irritation.

Elisabeth Aparecida[62] *et.al.,* developed and validated a dissolution test for glibenclamide tablets. Optimal conditions to carry out the dissolution test are 500 mL of phosphate buffer at pH 8.0, paddles at 75 rpm stirring speed, time test set to 60 min and using equipment with six vessels. The derivative UV spectrophotometric method for determination of glibenclamide released was developed, validated and compared with the HPLC method. The UVDS and HPLC methods showed good linearity at the concentrations of 5.0 – 14.0 and 8.0 – 12.0 µg/mL, respectively. The least square regression showed excellent correlation coefficient r^2 = 0.9999 (UVDS) and r^2 = 0.9988 (HPLC). Precision and recoveries were 0.42% and 100.25%, respectively.

Mohamed Hassan[63] *et.al.,* formulate and evaluate polymeric matrices and membrane systems for their potential use as transdermal drug delivery devices. Polymers such as EC, PEG 6000, PVP, HPMC, Eudragit RLPM and Eudragit RSPM were employed. Plasticizers such as Glycerol and Dibutylphthalate were incorporated as a model drug. Ephedrine Hydrochloride was incorporated as a model drug. Drug containing films were evaluated for thickness, uniformity, weight variation, area variation and drug content uniformity, K-C type diffusion cell was used to study *in vitro* drug release from matrices and membrane systems. The rate of release of ephedrine hydrochloride from Eudragit RLPM: RSPM 60:40 were found to be faster than from 40:60, than from 20:80, combinations of Eudragit RLPM and Eudragit RSPM respectively.

Bhalla H.L[64] *et.al.,* designed suitable matrix type polymeric films containing drug reservoir, which could form the basis of a controlled release transdermal formulation. Films were prepared using PVA and PVP along with plasticizers like glycerol and PEG. The flux of chlorpheniramine maleate was determined across guinea pig, rabbit and human cadaver skin using a Valia-Chien type diffusion cell. The flux of drug was found to be 0.12±0.08, 0.93 ±0.01. 0.006 ± 0.002 mg/cm^2/hr through guinea pig, rabbit and human cadaver skin respectively. The transdermal permeability was found to be 0.48, 3.72, 0.024cm/hr X 10^{-3} through guinea pig, rabbit and human cadaver skin respectively indicating that the drug was capable of being transported through the skin.

Kanikkannan N[65] *et.al.,* employed solution casting method using both glass and mercury substrate was used for the preparation of indomethacin patches . K –C type diffusion cell was used for *in-vitro* release studies. The PVA-PVP patches released 100% drug within the 24 hrs period of study. Eudragit RL100-PVP (8:2) with PEG 400 as plasticizer yielded smooth and flexible patches with good release profiles. The release of drug from many of the Eudragit based patches followed the diffusion controlled Higuchi's model. In conclusion, the combinations of PVA-PVP and Eudragit RL100-PVP matrices may potentially be developed as a transdermal therapeutic system.

Ramesh Gannu[66] *et.al.,* developed 10 nitrendipine formulations composed of Eudragit RL 100 and HPMC in the ratios of 5:0, 4:1, 3:2, 1:4 in formulations and Eudragit RS 100 and HPMC in the same ratios with 6%v/w of carvone as penetration enhancer,15% v/w of PEG as plasticizer in dichloromethane and methanol as solvent system. The prepared TDDS were evaluated for *in vitro* release, *ex vivo* permeation, moisture absorption, and moisture content and mechanical properties. The drug release in 24hrs for Eudragit RL100: HPMC and Eudragit RS100: HPMC were 89.2% and 86.1% respectively. Again formulations Eudragit RL100: HPMC and Eudragit RS100: HPMC (flux 23.51mcg/hr/cm^2 and 22.98mcg/hr/cm^2respectively) showed maximum skin permeation.

Jamakandi V.G[67] *et.al.,* evaluated the possibility of using different polymeric grades of HPMC (6cps, 15cps, and K4M) for the development of TDDS of Nicorandil, an antianginal drug. Prepared matrix type patches were evaluated for their physicochemical characterization followed by *in vitro* evaluation. Selected formulations were subjected for their *ex vivo* studies on porcine ear skin. Among the different HPMC formulations, transdermal patch with 6cps and 6% w/v DMSO as permeation enhancer showed maximum release and offered least resistance to the movement of drug molecules due to its high hydrophilic nature and high water permeability value to water.

Wagh M.P[68] *et.al.,* formulated transdermal films with hydrophilic polymers (PVA, PVP). Study was undertaken to report film forming properties of the polymers used and *in vitro* drug release from monolithic matrices. The drug loading was performed at 0.1% w/w and 0.01% w/w based on the weight of polymers. It was found that PVP, PVA along with glycerin as plasticizer have good film forming properties. Drug release followed zero order kinetics.

Rajagopal K[69] *et.al.,* prepared matrix type transdermal patches of nimesulide by using different polymers alone or in combination, (HPMC,EC,MC) dibutyl phthalate as a plasticizer and aluminium foil as a backing membrane. *In vitro* studies through cellophane membrane and excised mice skin in phosphate buffer (pH 7.4) showed that HPMC: EC (2:2) combination may be a suitable polymer combination for development of transdermal drug delivery system of nimesulide.

Ubaidulla U[70] *et.al.,* studied the improvement of permeability of carvedilol from transdermal films, which is made by HPMC as polymeric matrix and propylene glycol as plasticizer. SLS, Tween 20, DMSO and PEG 400 were used as permeation enhancers. Skin permeation was studied by Franz diffusion cell using excised rat abdominal skin. The effect of iontophoresis on permeation of carvedilol transdermal films were studied alone and mixed with enhancers. The permeation enhancers and iontophoresis synergistically enhanced permeability of carvedilol from its films.

Marcela Ramírez[71] *et.al.,* evaluated different variables that influence drug release from hydrated hydrophilic matrices, the polymer proportion, the drug dose and the matrix pH can be included. These variables have been used to modify the drug release rate and to examine its effect on the release mechanism. Hydrated matrices were prepared varying the matrix proportion of HPMC, the pH and the amount of verapamil hydrochloride loaded. The matrices release behavior was examined using 900 mL of an aqueous solution of NaCl (0.9%) as dissolution medium. The increase of the HPMC matrix proportion reduced the release rate of the drug. The release profiles showed zero order kinetics for drug dissolution proportions up to 70%. The increase of the matrix pH from 5.0 to 8.0 increased the release rate.

Sara Nicoli[72] *et.al.,* investigated *in vitro*, the kinetics of release and permeation of caffeine, chosen as model drug, from bioadhesive transdermal films. Permeation experiments were performed from films with different drug loadings using rabbit ear skin as barrier. In order to characterize the release kinetics of caffeine from the film, a polyethylene membrane, impregnated with IPM was employed. The data obtained in the present work suggest that caffeine release from transdermal bioadhesive films was controlled either by the permeability characteristics of the skin or by the film itself, depending on drug loading. When drug loading is low (i.e., caffeine is dissolved in the polymers constituting the film), the control resides in the skin. When caffeine loading exceeds its

solubility in the film, the permeation profile is not linear, but shows a sort of burst effect.

Kumar R[73] *et.al.,* gave an insight into the considerable potential of lecithin organogels (LO's) in the applications meant for topical drug delivery. These systems are currently of interest to the pharmaceutical scientist because of their structural and functional benefits. Being thermodynamically stable, LO's are prepared by spontaneous emulsification and therefore possess prolonged shelf life. The utility of this novel matrix as a topical vehicle has further increased owing to its very low skin irritancy potential. Varied aspects of LOs viz formation, composition, phase behavior, and characterization have been elaborated, including a general discussion on the developmental background.

Saeed Arayne M[74] *et.al., The in vitro* availability studies of glibenclamide in presence of commonly used antacids are present in this paper. Glibenclamide is used for the treatment of NIDDM and antacids are prescribed to encounter gastric acidity etc. These studies were carried out in simulated gastric juice and in buffer of pH 7.4 at 37 and 48°C. Aluminum hydroxide, aluminum trisilicate, magnesium oxide, magnesium trisilicate, sodium bicarbonate, calcium carbonate, magaldrate and simethicone (2,4-dimethoxypolysiloxane) antacids were used in these studies.

Sakellarioul P[75] *et.al.,* studied the interactions and partitioning of glycerol in PVA, HPMC and their blends has been studied by means of torsional braid analysis (TBA). Glycerol was shown to be more efficient plasticizer for PVA than HPMC in agreement with solubility parameter prediction. Kelley-Bueche-type equations were fitted to the experimental Tg data and initial slopes yielded an interaction parameter, Ks, between glycerol and the two polymers. The compositions of the two plasticized phases were calculated from Kelley Bueche expressions fitted to the experimental data, enabling determination of the glycerol partition coefficients into the two phases. In blends with 20-60% PVA, glycerol partitioned selectively into the PVA-rich phase whereas in the system with 80% PVA, glycerol partitioned selectively into the HPMC-rich inclusions.

Sadashivaiah R[76] *et.al., prepared* matrix-type transdermal drug delivery systems of haloperidol lactate using different ratios of EC: PVP (3:2, 2:3, 4:1, 1:2, 2:1, and 1:4) by solvent-evaporation technique. Physicochemical parameters were characterized, and dissolution studies of the formulated films were performed. In addition, solubility studies at various values of pH were carried out, and partition coefficient in octanol/water system, flux, and enhancement ratio were also evaluated. *In vitro* permeation studies were done using modified Franz diffusion cells through human cadaver skin utilizing 20% PEG 400 in normal saline. Higuchi and Peppas models were used for optimizing the formulation.

Ting Li[77] *et.al.,* evaluated the enhancing effects of the permeation enhancers using two-chamber side-by-side diffusion cells containing excised rat skin. DSC was used to evaluate the compatibility between indomethacin and MASCOS 10. Tack, shear strength and peel strength were measured to estimate the adhesion of the patch because the adhesive is critical for the safety, efficacy and quality of the product. The drug content and drug release rate of the patch are also essential standards in industrial process, so the work was complicated. It was notable that the presence of IPM, oleic acid and Tween 80 did not increase indomethacin permeation from the transdermal patches compared with the transdermal patches containing azone and L-menthol ($P > 0.05$).

Lai Wah Chan[78] *et.al.,* selected six grades of polyvinyl alcohol (PVA), PVA V (degree of hydrolysation 99.45%, mol. wt 140000—150000) and PVA VI (degree of hydrolysation 98—99%, mol. wt 85000—146000) for combination with PVA I (degree of hydrolysation 99%, mol. wt 17300) to prepare composite films with different amounts of PVA I and film thickness. The permeability coefficients increased with the amount of PVA I in the PVA V–I films. Conversely, the presence of PVA I in the PVA VI–I films decreased the permeability of the composite films to diclofenac sodium. The results indicated that PVA I content in the composite films was a critical factor, affecting the apparent solubility and/or swelling properties, and thereby permeability of the composite films.

Sridevi S[79] *et.al.,* developed acrylate based transdermal drug delivery system (TDDS) for glibenclamide and evaluate it for its pharmacodynamic performance in male wistar rats. The drug embedded in a polymeric matrix of polymethyl methacrylate and EC was evaluated for its hypoglycemic activity in normal and streptozotocin induced diabetic rats in comparison with its oral therapy. A glucose tolerance test (GTT) was conducted in oral, TDDS and control group. TDDS significantly sustained the hypoglycemic activity for 24hrs in normal rats when compared to oral administration where the effect declined after 8 hrs.

Frankum James[80] *et.al.,* discussed the ability of PLO to enhance bioavailability of drugs, clinical studies with topical nonsteroidal anti-inflammatory drugs, pharmacokinetics of nonsteroidal anti-inflammatory drugs following topical application, side effects, and instructions for use. They conclude that PLO provides a topical vehicle base for delivery of analgesic drugs with the advantages of significant reduction of severe side effects, increased patient compliance and increase of potential analgesic effects at the painful site.

Laura Lee Sartor[81] *et.al.*, determined whether transdermal methimazole was as safe and effective as oral methimazole for the control of hyperthyroidism in cats. Forty-seven cats with newly diagnosed hyperthyroidism were randomized to receive either transdermal methimazole in PLO, or oral methimazole. Cats were evaluated at weeks 0, 2, and 4. Data between the 2 groups and over

time were compared by nonparametric methods. Although the overall efficacy of transdermal methimazole is not as high as that of oral methimazole at 2 weeks of treatment, it is associated with fewer GI adverse effects compared to the oral route.

Pandey MS[82] *et.al.,* formulated and evaluated the suitability of PLO containing flurbiprofen for topical application. Four formulations were developed using flurbiprofen, lecithin, Pluronic F127, isopropyl palmitate, water, sorbic acid and potassium sorbate were coded as FL1, FL2, FL3 and FL4. All the formulations carried 30% w/w of lecithin phase and 70% w/w of Pluronic phase. The formulated organogels were evaluated for appearance and feel psychorheologically, *in vitro* diffusion study, drug content, viscosity and pH. Release of flurbiprofen from all formulations was monitored via dialysis membrane-70 and Wistar rat skin as a semi permeable membrane into phosphate buffer saline (0.2 M, pH 7.4) using K-C diffusion cell.

Ursula Krotscheck[83] *et.al.,* evaluated transdermal administration of morphine and fentanyl using a pluronic lecithin organogel in dogs. IV administration of morphine and fentanyl resulted in therapeutic serum drug concentrations. Following transdermal administration, however, median serum drug concentrations were never above the limit of quantitation for morphine or fentanyl. These findings indicate that use of a PLO for transdermal administration of morphine or fentanyl cannot be justified.

OBJECTIVE

Transdermal Drug Delivery Systems (TDDS) have been available on the global market for more than 25 years as a successful alternative to systemic drug delivery for selected drug molecules. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. The advantages of transdermal drug delivery include its ease of use, patient compliance, sustained drug delivery, local application and safety. Oral medication must pass through the GIT, into the liver where the drugs are broken down, possibly lowering their effectiveness. With the transdermal formulation, drugs enter directly into the bloodstream, reducing the risk of gastrointestinal side effects and bypassing breakdown by the liver[5,84].

Diabetes is one of the leading causes of morbidity and mortality due to specific microangiopathy and the associated macroangiopathy. It is the leading cause of blindness and visual impairment in adults in the western hemisphere and the risk of cardiovascular disease is two to five times in persons with diabetes, as compared to normal adults. The vast majority of diabetic patients have Type 2 DM[47].

The prevalence of diagnosed diabetes has increased dramatically over the past 40 years both in the US and worldwide. In 1985, there were approximately 30 million people with diabetes worldwide; by 1995, this number had escalated to 135 million and

by 2025, it is projected that there will be an increase in the incidence of diabetes, affecting 300 million people. Most of the expected increase will be in type 2 diabetes, which accounts for >90% of cases of diabetes, while the incidence of Type 1 diabetes is anticipated to remain stable. By 2025 the countries with largest number of people with diabetes will be in India (>57 million, prevalence 6%), China (>37 million, prevalence 3.4%), and the United States (>21 million, prevalence 8.9%)[85].

Glyburide is a sulfonylurea type oral hypoglycemic drug commercially available in the field of drugs in the form of tablets. As of 2007, it is one of only two oral anti-diabetics in the World Health Organization Model List of Essential Medicines (the other being metformin)[86]. As of 2003, in the United States, it was the most popular sulfonyurea[87]. Additionally, recent research shows that glyburide improves outcome in animal stroke models by preventing brain swelling. A retrospective study showed that in Type 2 diabetic patients already taking glyburide there was improved NIH stroke scale scores on discharge compared to diabetic patients not taking glyburide. Glyburide formulated therein is a powerful drug, since it sometimes causes, a side effect, a significant and prolonged hypoglycemia, at a small dosage, so the dosage regimen should be specially attentioned[79]. Furthermore, since numbers of diabetes mellitus of aged people are recently increasing, the dosage is especially important in the administration of the oral hypoglycemic drug to aged people. Recently published data suggests that glyburide

is associated with significantly higher annual mortality when combined with metformin than other insulin-secreting medications[88].

In order to reduce the danger of the side effect as mentioned above, it is convenient that, if the drug can be made in the form of a percutaneously absorbable external skin treatment agent, the application amount can be easily adjusted and, in addition, even if rapid hypoglycemic action occurs, the agent can be easily removed or washed out and therefore, the danger can be avoided.

PLAN OF WORK

The work entitled Formulation, evaluation and *in vitro* permeation studies of transdermal glyburide from matrix type patches and PLO gels was planned and carried out for a period of 9 months (May 2009- January 2010) in the following manner.

Phase I : Literature survey
Design of the study

Phase II : Preparation of the standard graphs
Preparation of glyburide transdermal patches and PLO gels

Phase III : Evaluation of prepared patches and Gels

Compatibility studies using IR spectrophotometer.
Physico- chemical parameters of the patches.
Characterization of PLO.

Phase IV :

In vitro drug permeation studies of transdermal formulation

Stability studies.

Data analysis and project submission.

MATERIALS AND EQUIPMENTS USED

Table: 4. Materials Used

S. No	Material	Source
1	Glyburide	Gift sample from Micro Labs, Bangalore.
2	Polyvinyl alcohol	Sigma Aldrich, Steinheim.
3	Poly vinyl pyrrolidone	Sigma Aldrich, Steinhem.
4	Glycerine	SD Fine Chemicals, Mumbai.
5	Dimethyl sulfoxide	Merck Ltd.
6	Ethylcellulose	SD Fine Chemicals, Mumbai.
7	Hydroxypropyl methyl cellulose	Himedia Laboratories, Mumbai.
8	Polyethylene glycol 400	Himedia Laboratories, Mumbai.
9	chloroform	Qualigens fine chemicals, Mumbai.
10	Methanol	SD Fine Chemicals, Mumbai.
11	Mercury	SD Fine Chemicals, Mumbai.
12	Calcium chloride	Qualigens fine chemicals, Mumbai.
13	Potassium di hydrogen phosphate	Qualigens fine chemicals, Mumbai.
14	Sodium hydroxide	Qualigens fine chemicals, Mumbai
15	Sodium chloride	Qualigens fine chemicals, Mumbai.
16	Pluronic F-127	Sigma Aldrich, Steinheim.
17	Lecithin soya	Himedia laboratories Pvt. Ltd, Mumbai.
18	Potassium sorbate	Himedia Laboratories Pvt Ltd, Mumbai.
19	Sorbic acid	Himedia Laboratories Pvt Ltd, Mumbai.
21	TLC plates	Merck Ltd.
22	Cyclohexane	Hi-pure fine chem Industries, Chennai.
23	Glacial acetic acid	Qualigens fine chemicals, Mumbai.
24	Sodium lauryl sulfate	***Sigma*** Chemicals, Steinheim.
25	Tween 80	Indian research products, Mumbai.
26	Cellophane membrane	Sartorius Ltd.

Table: 5. Equipments used

S. no	Equipment	Model / Company
1	Franz Diffusion Cell	Fabricated one
2	UV-visible spectrophotometer	Jasco V-530
3	FT-IR spectrophotometer	Jasco-FT-IR 8201 PC
4	Digital balance	Denver instruments
5	Dissolution test apparatus	Lab India disso 2000
6	Hot air oven	Inlab equipments
7	Magnetic stirrer	Remi equipments
8	Circular mould dishes	Fabricated one
9	Laboratory stirrer with variable speed control	Remi motors
10	Vacuum desiccator	-
11	Dial caliper	Aerospace electronic digital micrometer
12	Single pan balance	Dhona 200 D

METHODOLOGY

Glyburide, an important drug of sulfonylurea class, is currently available for treating hyperglycemia, but has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy. Since these drugs are usually intended to be taken for a long period, patient compliance is also very important. In order to reduce the danger of the side effect as mentioned above, it is convenient that, if the drug can be made in the form of a transdermal formulation.

Preformulation studies:

Before the formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically characterized. Preformulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of dosage forms.

In the present work, pre- formulation studies on the compatibility between drug and polymer were carried out using thin layer chromatography and Infra- Red spectroscopy.

THIN LAYER CHROMATOGRAPHY:

A thin layer chromatography was carried out to study interaction between the drug and polymers. For this the pure drug and its combinations with the polymers were subjected to chromatographic studies.

The following TLC system was used:

Precoated TLC plates	:	Mfg by S.d fine chemicals
Adsorbant layer	:	Silica gel G
Layer thickness	:	200mμ
Separation technique	:	Ascending
Size	:	10x20cm
Mobile phase	:	

Chloroform: cyclohexane: ethanol: glacial acetic acid[89]

45 : 45 : 5 : 5

Preparation of samples : a suitable amount of pure drug or equivalent amount of the samples were dissolved in chloroform: methanol (1:1) and were used for spotting.

Amount applied	:	10μL
Detection	:	UV chamber

The Rf values are given in the table:8. and figure:6.

FT/IR Spectral studies

Compatibility studies of the drug and the polymers were carried out using FT/IR JASCO-410 spectrometer. 1 part of the sample is mixed thoroughly with 3 parts of dried potassium bromide and it was compressed into transparent thin pellets. The pellets were scanned under IR region and the spectra were recorded and discussed in the later part.

ESTIMATION OF GLYBURIDE:

The following methods are available for the estimation of glyburide

UV spectrophotometric method[74].

LC –MS method Z

HPLC method[90]

RPHPLC method [91]

Simultaneous estimation of glyburide, gliclazide, glipizide, pioglitazone, repaglinide and rosiglitazone by HPLC[92].

Simultaneous Estimation of Glyburide and Metformin HCl using UV – visible spectroscopy[93].

In the present study, to increase the sensitivity of the assay method, UV method was selected for the analysis of glyburide. The UV method is simple and accurate, glyburide exhibits strong absorption at 300 nm respectively (BP 1998).

PREPARATION OF STANDARD GRAPH OF GLYBURIDE:

Standard stock solution:

The stock solution (1mg/ml) of glyburide was prepared in phosphate buffer solution (pH7.4).

Scanning of glyburide:

The above prepared standard stock solution was scanned under UV region between 200- 400nm and 300nm is found to be the absorption maxima wavelength and same was used for further analysis.

Standard plot:

From the standard stock solution a series of dilutions were made in such a way to obtain 5, 10, 15, 20, 25 µg/ml concentrations, using phosphate buffer pH 7.4. The linearity of Glyburide was found to be ranging from 5,10,15….50µg/ml. The absorbance were measured against the reagent blank (phosphate buffer

pH 7.4) using SHIMADZU UV 1700 spectrophotometer at 300nm and were given in the table:9. & figure:16. Calibration graph was plotted against respective drug concentration versus absorbance at 300nm[74].

FORMULATION OF TRANSDERMAL PATCHES

General method of preparation of transdermal patches

In the present study, matrix type transdermal patches of glyburide were prepared by moulding techniques. A flat circular glass moulds having diameter 4.5cm and height of 1cm with a total surface area of 15.91cm^2 was fabricated for this purpose.

Preparation of casting solutions[94,66]

The polymeric solution were prepared by dissolving the PVA and PVP combination in water in the ratio 8:2, 6:4, 10:0, 8:0, 0:8, 0:6. Similarly the polymeric solution of HPMC and EC combination were prepared by dissolving the combination in alcohol: chloroform mixture (1:1) in the ratio 2:2, 3:1, 4:0, 3:0, 0:4, 0:3. Glycerine was used as plasticizer and DMSO, SLS, Tween 80 as penetration enhancers. Weighed amount of drug was dispersed in each of the polymeric solutions while stirring to ensure the uniform distribution of drug. The composition of transdermal patches were listed in the table:6. It was placed aside without any disturbances to allow the entrapped air to bubble out.

Table:6. COMPOSITIONS OF TRANSDERMAL PATCHES OF GLYBURIDE

Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Glyburide (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Glycerin in %w/w	20	20	20	20	20	20	20	20	20	20	20	20	20	20
DMSO % w/w	5	5	5	5	5	5	5	5	5	5	5	5	-	-
Tween 80 % w/w	-	-	-	-	-	-	-	-	-	-	-	-	5	-
SLS % w/w	-	-	-	-	-	-	-	-	-	-	-	-	-	5
PVA in parts	8	6	10	8	-	-	-	-	-	-	-	-	-	-
PVP in parts	2	4	-	-	8	6	-	-	-	-	-	-	-	-
HPMC in parts	-	-	-	-	-	-	2	3	4	3	-	-	2	2
EC in parts	-	-	-	-	-	-	2	1	-	-	4	3	2	2

Table: 7. FORMULATION COMPOSITION OF PLO GELS

Contents %	F15	F16	F17	F18	F19
Glyburide (mg)	5	5	5	5	5
Ethanol (ml)	10	10	10	10	10
Soya lecithin in parts	2	3	5	7	3
Sorbic acid (g)	0.2	0.2	0.2	0.2	0.2
Iso propyl palmitate upto (ml)	100	100	100	100	100
Pluronic F-127 in parts	20	20	20	20	30
Potassium sorbate (g)	0.2	0.2	0.2	0.2	0.2
Purified water upto (ml)	100	100	100	100	100

EVALUATION OF TRANSDERMAL PATCHES

Physical appearance:[67]

All the transdermal patches were visually inspected for color, clarity, flexibility, and smoothness.

Folding endurance:

A strip of film (4 × 3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Thickness of the films:

The thickness of the drug-loaded polymeric films were measured at 5 different points using a digital micrometer. The average and standard deviation of 5 readings were calculated.

Weight uniformity:

The films of different batches were dried at 60°C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights.

Average weight of each patches = total weight of 5 patches/ 5

Standard deviation =

Where x = weight of individual patch.

X = average weight.

n = number of patches.

Percentage moisture uptake:

The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride.

Finally, the films were weighed and the percent moisture uptake was calculated using the formula

Percentage moisture uptake =
[Final weight - Initial weight/Initial weight] × 100

Percentage moisture content

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. The films were again weighed and the percentage moisture content was calculated using the formula

Percentage moisture content =
[Initial weight - Final weight/Final weight] × 100

Flatness:

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness. The physico- chemical parameters of the transdermal patches were shown in table: 10,11.

Swelling Ratio Measurement [60]

Preparation of Disc-Like Specimens

Discs of the polymers used were prepared by compressing 500 mg of powder using flat-faced punches 12 mm in diameter to yield a hardness of 100 N ± 10. Before swelling tests, the diameter and height of each tested disc were measured.

Swelling Studies

Swelling studies were performed by placing the polymeric discs in petridishes at 37°C and measuring their thickness as a function of time during swelling. The swelling ratios of different polymers were given in the table:12. & figure:17.

***In vitro* drug release studies**

A Paddle over disc assembly (USP XXIII, Apparatus 2) was used for the assessment of release of drug. The TDDS patch was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml phosphate buffer of pH 7.4. The apparatus was equilibrated to 37 ± 0.5°C and operated at 50 rpm. The samples (5 ml aliquots) were withdrawn at appropriate time intervals up to 8 hours and analyzed on a UV spectrophotometer at 300nm. The release profiles of formulations were shown in table: 14,15. & figure: 18,19.

CHARACTERIZATION OF PLO

Viscosity:[82]

Viscosities of the formulated organogels were determined using Brookfield viscometer with Spindle no.7 (Model: RV DV-I) at 25°C with the spindle speed of 10 rpm.

pH:

The pH of formulated organogels was determined using pH meter. The electrode was immersed in organogels. Readings were recorded on pH meter and were shown in the table: 13.

EVALUATION OF TRANSDERMAL SYSTEMS

Drug content

Transdermal patches of specified area (3.066 cm^2) was cut into small pieces and PLO formulation of 0.5 g was taken into a 50 ml volumetric flask and 25 ml of phosphate buffer pH 7.4 was added, gently heated to 45°C for 15 minutes, and kept for 24 hours with occasional shaking. Then, the volume was made up to 50 ml with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free formulation. The solutions were filtered through Whatman filter paper No. 42 and the absorbance was measured at 300 nm.

In vitro permeation:

The permeation experiments were performed at 37°C using Franz diffusion cells as shown in figure: 5. A cellophane membrane was mounted in the diffusion cell having across sectional area of 3.14 cm^2. The membrane was tightly secured between the donor and receptor compartments. The upper surface of the membrane was exposed to solution of drug formulation. The receptor compartment was filled with 14.5 ml of isotonic phosphate buffer pH 7.4. The donor compartment was sealed to prevent evaporation of the test formulation. The franz diffusion cells was connected to thermostatic circulating water bath through stainless steel pipes allowing circulation of water through the water jacket surrounding the cell. A volume of 1.0 ml was withdrawn from the receptor compartment from each cell after each hour after application of the test

formulation. The withdrawn sample was immediately replaced by freshly prepared buffer solution. The samples were analyzed in UV spectrometer at 300nm[95] and shown in the table: 16-18 & figure:20-22.

Figure:5.

STABILITY STUDY[96]

The prepared patches and gels were subjected to stability study by storing the formulations at different storage conditions. The formulations were stored for one month at different temperature i.e 40°C and at room temperature (25°C). The stability study was conducted with regard to moisture content, moisture uptake, thickness, weight variation, folding endurance, flatness, *in vitro* dissolution, drug content for the patches and pH, viscosity, drug content for the gel formulation. The formulations, which retained their physical properties, were further subjected to *in-vitro* permeation studies and were shown in the table:19-24 & figure:23.

Transdermal drug delivery system of glyburide was developed using polymers like PVA, PVP, HPMC EC employing glycerine as plasticizer and DMSO, SLS and Tween 80 as the permeation enhancers for transdermal patches and PLO gel was formulated using Pluronic F-127 and lecithin phase. Formulated patches were subjected to physico- chemical evaluations such as physical appearance, weight variation, thickness, % moisture content, % moisture uptake, flatness, and drug content, and the PLO formulation were tested for physical appearance, pH, and viscosity. The *in vitro* drug release studies across cellophane membrane were conducted and the best formulations were subjected to stability studies.

COMPATIBILITY STUDIES:

The compatibility studies confirmed that the absence of chemical interaction between drug and the polymers used. The physico- chemical parameters were evaluated.

Thin layer chromatography:

TLC for the pure drug and in combination with the polymers were performed as shown in figure:6. The Rf values were reported in the table:8. The Rf values indicate the absence of chemical interaction between the drug and the polymers used.

FT/IR Spectral studies

Compatibility studies of the drug and the polymers were carried using JASCO/FT/IR spectrometer and the spectras were given in the figure:7-15. The IR spectra obtained from the mixture of polymers and drug was matching with the spectra of the pure drug. There was no appearance or disappearance of any characteristic peaks, which confirmed the absence of chemical interaction between the drug and the polymer used.

Thin Layer Chromatogram Details:

Table:8. Rf values of drug and the polymers

S. no	SAMPLE	Rf VALUE
1	Drug	0.42
2	Drug + PVA +PVP	0.41
3	Drug + PVA	0.41
4	Drug +PVP	0.42
5	Drug + HPMC +EC	0.41
6	Drug + HPMC	0.42
7	Drug + EC	0.42
8	Drug + Pluronic F-127	0.42

Figure:6. TLC of Glyburide along with polymers

Figure:7. IR SPECTRA OF GLYBURIDE
Figure:8. IR spectra of POLYVINYL ALCOHOL
Figure:9. IR spectra of POLYVINYL PYRROLIDONE

Figure:10. IR spectra of HYDROXYPROPYL METHYL CELLULOSE
Figure:11. IR spectra of ETHYL CELLULOSE

Figure:12. IR spectra of PLURONIC F-127
Figure:13. IR spectra of PVA+PVP+GLYBURIDE
Figure:14. IR spectra of HPMC+ EC + GLYBURIDE
Figure:15. IR spectra of PLURONIC F-127 + GLYBURIDE
Fig:15. IR spectra of PLURONIC F-127 + GLYBURIDE

Table:9. Calibration graph of glyburide

Sl. No.	Concentration mcg/ml	Absorbance @ 300nm
1	5	0.2636 ± 0.02
2	10	0.5231 ± 0.01
3	15	0.7820 ± 0.04
4	20	1.0250 ± 0.02
5	25	1.2811 ± 0.05

Figure:16. Calibration graph of glyburide

Calibration curve : linear

Expression : Abs = A + B* Conc

Factor : A = 0.0139

B = 0.0507

Coefficient : 0.999935

PHYSICO- CHEMICAL PARAMETERS

Transdermal patches

The results of the physico- chemical characterization of the fourteen patches were shown in the table: 10, 11. The weights obtained by the formulated transdermal patches were between 0.28g and 0.57g.

For all the formulation the thickness varied between 0.11 to 0.16mm. The low values for standard deviation indicate physical uniformity of the patches.

The moisture uptake studies revealed that all the formulated transdermal patches were having the low moisture uptake and moisture content when compared with formulations F5 and F6. The reason for increase in moisture uptake and content for F5 and F6 may be attributed to the hygroscopic nature of the polymer, where F11, F12 transdermal patches has the least moisture content and uptake due to the hydrophobic nature of the polymer.

Percentage of swelling index for all the polymers used in transdermal patches were between 0.5 - 13.9%. The order of increasing swelling index of the polymers are as follows, PVP > HPMC > PVA > EC. The results are given in the table:12 & figure:17.

Table:10. Physico-chemical parameters of the formulated transdermal patches of glyburide- F1 to F7

Parameters	F1	F2	F3	F4	F5	F6	F7
Physical appearance	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent
Weight variation(g)	0.55 ±0.01	0.42 ± 0.01	0.57 ± 0.1	0.55 ± 0.08	0.19 ± 0.06	0.18 ± 0.01	0.35 ± 0.04
Thickness (mm)	0.14± 0.008	0.16± 0.001	0.13± 0.004	0.12± 0.012	0.14± 0.007	0.16± 0.009	0.16± 0.008
%moisture uptake	20.7	26.7	20.1	30.5	72.5	54.3	25.3
%moisture content	2.9	3.0	2.2	1.4	3.6	3.6	3.3
Folding endurance	350	361	348	340	375	360	245
%Drug content	101.1	100.7	99.7	100.1	99.2	100.3	99.8
%Flatness	99.9	99.9	100	100	99.8	99.9	99.9

Table: 11. Physico-chemical parameters of the formulated transdermal patches of glyburide- F8 to F14

Parameters	F8	F9	F10	F11	F12	F13	F14
Physical appearance	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent
Weight variation(g)	0.34 ± 0.06	0.31 ± 0.05	0.29 ± 0.01	0.42 ± 0.03	0.40 ± 0.06	0.36 ±0.02	0.35 ±0.01
Thickness (mm)	0.13± 0.006	0.13± 0.004	0.13± 0.011	0.11 ± 0.004	0.11 ±0.001	0.16 ± 0.001	0.16 ± 0.003
% moisture uptake	25.6	26.9	27.3	1.2	1.0	24.9	25.0
% moisture content	3.1	2.3	1.8	0.46	0.5	3.0	3.2
Folding endurance	256	278	265	155	175	245	245
% Drug content	100.5	99.8	98.5	100	99.3	100.0	99.8
%Flatness	100	99.5	99.8	99.8	100	100	100

Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. Folding endurance was in the range of 155 to 375, transdermal patch F11 representing the least value, due to the brittle nature of EC and F5 has the maximum folding endurance due to the hydrophilic nature.

Good uniformity of drug content among the batches were observed with all formulations and ranged from 98.5% to 101.1%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability.

The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating ~100% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin.

From the *In vitro* dissolution and diffusion studies it was found that F7 formulation showed better release pattern when compared with the other formulations. This is due to the addition of hydrophilic component HPMC to an insoluble film former EC, where HPMC tends to enhance the release, and EC sustains the release rate. Among the permeation enhancers used formulation F7 containing DMSO as permeation enhancer showed a better release pattern when compared with the formulation F13 and F14 which contains Tween 80 and SLS respectively. The results were given in

the table:14-17 & figure:18-21. An increase in the proportion of PVP polymer caused an increase in the amount of drug diffused causing a initial bursting release, as they are permeable to aqueous medium but the films were sticky and difficult to handle when it absorbs moisture. F11, F12 showed the least release due to minimum swelling and showed higher resistance to the permeation of lipophilic drug due to its hydrophobic nature.

Pluronic lecithin organogel:

Increase in lecithin content increases the viscosity of the formulation and this might be due to the formation of complex networks. Formulation F18 with 7% lecithin has maximum viscosity. Further increase in concentration of lecithin decreased the cumulative percent drug release which might be due to the extensive formation of network like structure with very high velocity. The formulation F16, containing 20% pluronic and 3% lecithin showed higher cumulative percent drug release as shown in the table:18 & figure:22. The pH of all the formulations was around the skin pH (5.81 to 6.65) and was smooth and free from grittiness. The drug content of gels ranged from 98.6 -100.8% and were reported in the table:13.

Table:12. % SWELLING INDEX OF POLYMERS USED IN TRANSDERMAL PATCHES

POLYMERS	% S.I
PVA	5.6
PVP	13.9
HPMC	12.2
EC	0.5
PVA:PVP 8 : 2	5.8
PVA:PVP 6 : 4	6.8
HPMC:EC 2 : 2	3.9
HPMC:EC 3 : 1	7.6

Table:13. EVALUATION STUDIES OF PLO GELS

Evaluations	F15	F16	F17	F18	F19	F20
pH	5.81	6.52	6.11	6.65	5.99	6.43
Viscosity (poise)	2932	3204	3360	3436	2804	2752
% Drug content	98.63	100.79	100.22	100.87	100.11	99.16

Figure:17. % SWELLING INDEX OF POLYMERS USED IN TRANSDERMAL PATCHES

Table:14. *In vitro* dissolution studies from transdermal patches F1- F7

Formulation code	Cumulative percentage release of drug at							
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
F1	5.11± 0.09	11.62± 0.08	22.36± 0.01	26.42± 0.05	37.61± 0.06	40.29± 0.05	42.32± 0.04	46.49± 0.05
F2	10.36± 0.01	12.27± 0.01	16.32± 0.03	21.27± 0.07	39.36± 0.04	42.66± 0.04	49.39± 0.01	51.34± 0.06
F3	3.61± 0.02	6.23± 0.03	13.84± 0.06	27.98± 0.03	36.65± 0.01	39.53± 0.01	47.18± 0.06	49.97± 0.06
F4	1.18± 0.04	2.64± 0.03	4.89± 0.08	10.17± 0.04	21.63± 0.09	28.54± 0.06	31.98± 0.01	34.21± 0.02
F5	22.23± 0.05	23.59± 0.05	26.87± 0.01	29.68± 0.05	30.42± 0.03	30.88± 0.02	31.21± 0.02	32.36± 0.01
F6	18.51± 0.08	20.27± 0.04	21.68± 0.1	24.96± 0.01	27.84± 0.12	29.62± 0.01	30.34± 0.03	34.9± 0.01
F7	5.01± 0.04	10.81± 0.03	15.29± 0.09	22.38± 0.05	29.77± 0.03	36.54± 0.05	41.61± 0.04	48.74± 0.04

Figure:18. *In vitro* dissolution profile of formulated transdermal patches F1- F7

Table:15. *In vitro* dissolution studies from transdermal patches F8- F14

Formulation code	Cumulative percentage release of drug at							
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
F8	3.00± 0.08	5.81± 0.04	9.62± 0.01	21.44± 0.03	22.93± 0.01	29.77± 0.12	49.88± 0.03	56.61± 0.05
F9	0.9± 0.04	1.00± 0.04	3.00± 0.08	6.00± 0.01	17.64± 0.08	26.98± 0.04	30.66± 0.04	31.52± 0.08
F10	2.97± 0.01	4.44± 0.05	5.32± 0.04	7.39± 0.08	13.44± 0.03	29.68± 0.05	32.47± 0.09	33.11± 0.04
F11	0.81± 0.03	0.92± 0.06	1.99± 0.08	3.82± 0.07	3.88± 0.06	07.79± 0.06	9.38± 0.01	11.45± 0.03
F12	1.04± 0.01	1.29± 0.07	1.68± 0.01	2.34± 0.04	5.86± 0.02	06.33± 0.05	6.59± 0.03	11.63± 0.02
F13	4.99± 0.02	11.43± 0.08	13.12± 0.02	20.68± 0.03	25.14± 0.02	30.44± 0.07	40.73± 0.04	45.66± 0.03

F14	3.66± 0.03	8.74± 0.09	10.67± 0.05	15.96± 0.05	21.36± 0.01	27.47± 0.02	37.81± 0.05	43.45± 0.04

Figure:19. *In vitro* dissolution profile of formulated transdermal patches F8- F14

Table:16. Cumulative percentage permeation studies from transdermal patches F1 – F7

Formulation code	Cumulative percentage release of drug at							
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
F1	18.34± 0.02	21.89± 0.05	24.69± 0.06	25.63± 0.01	26.29± 0.05	30.32± 0.05	56.18± 0.01	64.99± 0.01
F2	19.23± 0.07	27.21± 0.06	31.35± 0.09	35.01± 0.03	41.86± 0.06	47.74± 0.09	57.28± 0.02	65.54± 0.04
F3	2.68± 0.06	2.95± 0.01	5.42± 0.06	8.37± 0.04	10.04± 0.01	24.17± 0.04	32.64± 0.04	42.04± 0.05
F4	3.13± 0.02	4.72± 0.01	5.44± 0.04	8.12± 0.04	16.14± 0.1	31.00± 0.03	38.91± 0.04	63.24± 0.06
F5	43.08± 0.01	43.68± 0.04	44.36± 0.02	44.96± 0.01	45.58± 0.04	46.18± 0.04	46.81± 0.09	47.40± 0.07

F6	40.30± 0.04	41.50± 0.05	42.37± 0.01	43.86± 0.03	45.17± 0.05	45.79± 0.06	46.39± 0.05	46.98± 0.08
F7	10.06± 0.03	20.45± 0.06	30.88± 0.02	37.54± 0.06	47.87± 0.07	56.99± 0.02	70.53± 0.04	74.45± 0.01

Figure:20. *In vitro* permeation profile of formulated transdermal patches F1- F7

Table:17. Cumulative percentage permeation studies from transdermal patches F8 – F14

Formulation code	Cumulative percentage release of drug at							
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
F8	8.06± 0.01	8.48± 0.03	18.77± 0.08	27.2± 0.03	34.16± 0.05	43.19± 0.01	48.49± 0.06	57.65± 0.05
F9	12.86± 0.04	24.11± 0.04	34.78± 0.04	42.15± 0.05	53.32± 0.05	57.38± 0.02	63.83± 0.01	68.80± 0.03
F10	9.49± 0.09	17.56± 0.03	26.46± 0.05	37.23± 0.06	51.05± 0.06	63.64± 0.03	65.13± 0.03	66.65± 0.04

F11	0.33± 0.04	0.6± 0.01	1.83± 0.05	2.54± 0.07	6.51± 0.02	7.06± 0.06	7.18± 0.04	7.74± 0.01
F12	0.39± 0.05	1.28± 0.03	1.38± 0.06	1.41± 0.01	1.57± 0.03	2.01± 0.05	4.08± 0.05	6.85± 0.02
F13	10.30± 0.01	16.70± 0.04	24.58± 0.03	36.08± 0.03	43.82± 0.01	49.90± 0.03	58.39± 0.07	72.42± 0.03
F14	9.19± 0.01	13.51± 0.02	28.02± 0.05	35.81± 0.03	41.86± 0.02	50.72± 0.01	57.51± 0.03	64.24± 0.03

Figure:21. *In vitro* permeation profile of formulated transderrmal patches F8- F14

Table:18. Cumulative percentage permeation studies from PLO gels F15 – F20

Formulation code	**Cumulative percentage release of drug at**							
	1 h	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**7 h**	**8 h**
F15	10.36± 0.03	12.49± 0.03	14.31± 0.04	19.26± 0.04	21.75± 0.03	30.55± 0.1	44.99± 0.1	50.23± 0.05

F16	24.75± 0.05	28.80± 0.05	33.67± 0.07	37.21± 0.03	46.3± 0.01	55.19± 0.09	62.62± 0.04	79.37± 0.06
F17	5.39± 0.06	10.23± 0.05	10.44± 0.03	10.85± 0.05	11.49± 0.09	18.7± 0.07	20.46± 0.01	25.69± 0.04
F18	2.47± 0.05	2.96± 0.04	4.24± 0.01	7.71± 0.06	10.39± 0.08	15.75± 0.03	22.09± 0.03	25.63± 0.08
F19	9.07± 0.03	10.21± 0.09	22.99± 0.02	29.09± 0.01	37.73± 0.04	45.39± 0.06	50.02± 0.06	67.27± 0.07
F20	5.49± 0.01	5.68± 0.06	11.72± 0.03	23.04± 0.03	35.85± 0.07	47.81± 0.01	50.06± 0.04	62.58± 0.03

Figure: 22. *In vitro* permeation profile of PLO gels F15- F20

Stability studies:

The selected formulations were stored at room temperature (25°C) and at 40°C for a period of 30 days and were assessed for any changes in their physico- chemical properties and *in vitro* diffusion through cellophane membrane. There was no appreciable difference in the diffusion pattern and physico- chemical properties of the formulations after 30 days and were shown in the table: 19-24 & figure :23.

Table:19. Physico- chemical parameters of the formulated transdermal patches during the stability studies at room temperature (25°C)

Parameters	F7	F8	F9	F13	F14
Physical appearance	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent
Weight variation (g)	0.354 ± 0.02	0.349 ± 0.04	0.309 ± 0.03	0.356 ± 0.01	0.351± 0.02
Thickness (mm)	0.166 ± 0.006	0.131± 0.004	0.137 ± 0.006	0.165 ± 0.002	0.165 ± 0.005
%moisture uptake	25.3	25.6	26.9	25	25.7
%moisture content	3.3	3.1	2.3	3.1	3.0
Folding endurance	245	256	277	243	241
%Drug content	99.8	100.1	100	99.6	100.4
%Flatness	100	100	99.9	100	99.9
% *in vitro* release	94.87	84.17	78.37	87.45	80.98

Table: 20. Cumulative percentage permeation studies from transdermal patches at room temperature (25°C)

Formulation code	Cumulative Percentage Release Of Drug at							
	1h	2h	3h	4h	5h	6h	7h	8h
F7	9.76 ± 0.02	20.58 ± 0.01	30.13 ± 0.04	31.42 ± 0.01	42.46 ± 0.07	51.86 ± 0.09	71.55 ± 0.07	74.74 ± 0.03
F8	8.26± 0.04	8.95± 0.02	15.55± 0.01	27.55± 0.01	33.57 ± 0.04	46.02 ± 0.03	52.84 ± 0.08	60.74 ± 0.11
F9	10.67 ± 0.05	20.74 ± 0.04	35.77± 0.04	42.15± 0.03	54.04± 0.03	56.98 ± 0.02	67.34 ± 0.02	70.10± 0.03
F13	10.01± 0.06	16.59 ± 0.04	25.26± 0.05	35.64 ± 0.01	43.94 ± 0.01	48.33 ± 0.01	58.88 ± 0.01	70.05 ± 0.04
F14	8.11± 0.02	12.62± 0.01	27.79± 0.03	36.34 ± 0.04	38.73 ± 0.03	46.14 ± 0.01	58.28 ± 0.01	63.51 ± 0.02
F15	9.73± 0.01	11.45 ± 0.07	14.29± 0.04	18.85 ± 0.02	19.90 ± _0.06	28.14 ± 0.02	42.40 ± 0.04	48.71± 0.04

F16	825.88± 0.01	28.44 ± 0.07	33.34± 0.04	36.87 ± 0.02	45.44 ± _0.06	56.73 ± 0.02	62.96 ± 0.04	77.64 ± 0.04

Table: 21. Evaluation studies of PLO gels at room temperature (25°C)

Formulation code	pH	Viscosity	Drug content
F15	5.8	2932	99.8
F16	6.5	3204	100

Table: 22. Physico- chemical parameters of the formulated transdermal patches during the stability studies at 40°C

Parameters	F7	F8	F9	F13	F14
Physical appearance	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent
Weight variation (g)	0.353 ± 0.02	0.349 ± 0.01	0.309 ± 0.03	0.356 ± 0.04	0.351 ± 0.01
Thickness (mm)	0.166 ± 0.003	0.131 ± 0.004	0.137 ± 0.007	0.165 ± 0.005	0.165 ± 0.007
% moisture uptake	25.3	25.6	26.9	25	25.0
% moisture content	3.2	3.0	2.2	3.0	3.0
Folding endurance	243	256	275	243	243
% Drug content	99.7	100	100	99.1	100
% Flatness	100	100	99.9	100	99.6
% *in vitro* release	93.22	82.10	78.37	86.92	80.07

Formulation code	Cumulative Percentage Release Of Drug at 1h	pH	Viscosity	Drug content
F7	9.7 ± 0.09			
F8	7.95 ± 0.08			
F9	12.47 ± 0.03			
F13	9.93± 0.09			
F14	8.83± 0.01			
F15	9.9± 0.01			
F16	25.14± 0.01			

Table:23. Cumulative

percentage permeation studies from transdermal patches at 40°C **Table:24. Evaluation studies of PLO gels at 40°C** **Formulation code**			
F15	5.7	2930	99.8
F16	6.3	3200	100

Figure: 23. COMPARATIVE CUMULATIVE PERCENTAGE PERMEATION OF GLYBURIDE FROM SELECTED FORMULATIONS DURING STABILITY STUDIES

SUMMARY AND CONCLUSION

An attempt to develop transdermal therapeutic system for glyburide was carried out for the purpose of attaining maximum bioavailability by tress passing pre-systemic hepatic metabolism and other side effects. The matrix type patches were prepared using four polymers namely PVA, PVP, HPMC, EC (F1- F14) and the PLO gels (F15-F20) were prepared by mixing the oil and aqueous phase.

The compatibility studies using TLC and IR spectral study revealed the absence of interaction between the drug and the polymers used.

The formulated transdermal patches (F1-F14) and PLO gels (F15-F20) were evaluated for the physico-chemical parameters, *in vitro* permeation and stability studies.

Transdermal patches

All the formulated transdermal patches were transparent, smooth and flexible in appearance. The patches showed a significant variation in their average weight, which might be due to the variation in the proportions of polymers used. There was no significant change observed in the thickness of all the fourteen patches.

The moisture uptake and moisture content studies revealed that all the formulated transdermal patches were having the low moisture uptake and moisture content when compared with the formulations F5 and F6. Polymer PVP showed the highest % S.I and low % S.I for EC polymer.

All the patches showed uniform drug content. The higher value of folding endurance can be attributed to the higher proportion of hydrophilic polymers. The patches exhibited ~100% flatness indicating no constriction.

Among the formulations prepared F7, F8, F9, showed a better *in vitro* drug release profile across the cellophane membrane. This might be attributed to the nature of polymer, plasticizer and permeation enhancer

used. Among the above mentioned formulations (F7, F8, F9), the F7 formulation which showed better release of drug was again evaluated by changing the penetration enhancers (F13, F14). The permeation rates of glyburide were arranged in the following increasing order: DMSO > Tween 80 > SLS. Transdermal patches F7 was better when compared to F13 and F14.

PLO gels

All the PLO formulations F15- F20 showed drug content in the range of 98.6% – 100.8% indicating uniform distribution of drug throughout the base. The viscosity of all the formulations was found to be in the range 2752-3455 poise. The pH of all the formulations was around the skin pH and found to be in the range of 5.81 to 6.65. All the formulations were smooth in feel and free from grittiness which increases the patient compliance. From the above studies it may be concluded that formulation F16, is an effective formulation for transdermal delivery, as it showed higher cumulative percent drug release and drug content.

Stability studies:

As far the above results were concerned formulations F7, F8, F9 ,F13, F14, F15, and F16 were selected and subjected for stability studies at room temperature (25°C) and at 40°C for a period of 30 days. The stability study results signified that the selected patches and gels possess adequate shelf life till 30 days.

Among the transdermal patches prepared formulation F7 containing HPMC and EC at 2:2 ratio with DMSO as penetration enhancer and formulation F16, PLO gel with 3% lecithin showed better combinations for the controlled release of glyburide. These formulations could be predicted to have continuous supply of glyburide at a desirable rate to systemic circulation, which improved day-to-day glycemic control in diabetic subjects. However long term pharmacokinetic and pharmacodynamic studies should be undertaken to establish the usefulness of these formulations.

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